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AUGUST, 1950

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PROCEEDINGS
OF THE
CHEMICAL SOCIETY

OFFICIAL ANNOUNCEMENTS

DEATHS.

The Council regret to announce the deaths of the following Fellows:

	Elected.	Died.
John Gerald Frederick Druce (S.W.16) ...	Feb. 18th, 1915.	June 22nd, 1950.
Francis William Gray (Aberdeen)	Feb. 18th, 1932.	July 2nd, 1948.
John Hanley (Newent)	May 2nd, 1901.	Apr. 18th, 1950.
Robert Haxwell Hicks (Cardiff)	Dec. 4th, 1930.	May 6th, 1950.
Gavin Lawson (Manchester)	Jan. 23rd, 1941.	Apr. 16th, 1950.
Terence Moore (Ilford)	Dec. 18th, 1941.	June 2nd, 1950.
Roland Victor Norris (Ceylon)	Dec. 2nd, 1909.	Apr. 28th, 1950.
Sir William Abraham Wayland (S.E.8) ...	Feb. 7th, 1901.	July 15th, 1950.

ELECTION OF NEW FELLOWS.

The following 43 candidates were elected Fellows of the Society on July 24th, 1950:

Harold Frank Simpson Addicott.
Harry Allsop.
Raizada Tapeshwar Nath Bali.
Geoffrey Thomas Barnes.
Cyril Arthur Beck.
Pushpa Mittra Bhargava.
Brian George Clist.
Henry Robert Conan.
Basil de Baskerville Darwent.
Cecily Darwin.
Paul De Mayo.
William Charles Dewey.
Edward Walter Felton.
Alan Fogg.
Michael Roy Foran.
William Cyril Frith.
Dennis Mario Green.
Carl David Gutsche.
Mrs. Thelma Eskin Habgood.
Francis Patrick Harrigan.
David Colin Havard.
Anthony Barrington Horlock.
Isobel Ann Kay.
Kenneth Emil Kolb.
Graham Ethelbert Lewis.
Rev. Wilfrid James Loughlin.
John Cooper Lunt.
Gerald William Goddard McDonald.
William Edwin McEwen.
Charles Gerard May.
Richard Louis Meier.
Alexander McBain Moore.
Bernard Francis Mullen.
Santi Ranjan Palit.
Brian Pearce.
William Robert Proops.
Osman Mohamed Ragheb.
Louis Soffer.
Gordon Clement Speers.
Bernard Ellis Stacey.
David Sloan Thirkell.
John Thomson.
Henry James Tinson.

RESEARCH FUND.

A meeting of the Research Fund Committee will be held in November next. All persons who have received grants, and whose accounts have not been declared closed by the Council, are informed that reports must be received by the Society not later than November 1st, 1950.

Applications for grants, to be made on forms obtainable from the General Secretary, must be received on or before November 1st, 1950. Applications from Fellows will receive prior consideration.

Attention is drawn to the fact that the income arising from the donation of the Worshipful Company of Goldsmiths is principally devoted to the encouragement of research in inorganic and metallurgical chemistry, and that the income from the Perkin Memorial Fund is to be applied to investigations relating to problems connected with the coal-tar and allied industries.

50th ANNIVERSARY OF THE DISCOVERY OF RADIUM.

The Society was represented at the Celebration of the 50th Anniversary of the Discovery of Radium held in Paris from July 16th to 20th by Professor F. A. Paneth who gave an Address at the opening ceremony in the name of all the delegates from overseas. The following Address was presented :

THE CHEMICAL SOCIETY
TO
L'ECOLE DE PHYSIQUE
ET CHIMIE

The President, Council, and Fellows of The Chemical Society send to the President and Members of the Organising Committee their sincere greetings on the occasion of the Celebration in Paris in July, One Thousand Nine Hundred and Fifty, of the Fiftieth Anniversary of the Discovery of Radium by Pierre and Marie Curie.

This fundamental discovery has led to a fuller understanding and knowledge of the nature of the matter from which the universe is composed. At the same time it marks the inception of a new era in our civilisation, the full effects of which have yet to be revealed.

We recall with pleasure and satisfaction that Marie Curie was elected an Honorary Fellow of the Chemical Society in 1904.

We desire to associate ourselves with our French colleagues and with Scientists throughout the world in paying homage to the memory of Pierre and Marie Curie and we send cordial greetings and best wishes for a most successful Meeting.

Signed on behalf of The Chemical Society.

ERIC K. RIDEAL, *President.*
W. A. AKERS, *Treasurer.*
D. H. HEY, } *Honorary*
H. BURTON, } *Secretaries.*

SCIENTIFIC PUBLICATIONS GRANT-IN-AID.

The Society has received through the Royal Society a grant for 1950 of £2,500 for publications and of £300 for capital expenditure on the Library from the Government Scientific Publications Grant-in-Aid.

GIFTS OF PUBLICATIONS.

The thanks of the Council have been conveyed to the following who had presented gifts of the Society's publications :—Dr. B. R. Carpenter, Miss E. M. Chatt, Mr. A. C. Clement, Mr. R. N. Doughty, Dr. T. H. Durrans, Mrs. K. East, Dr. S. I. Levy, Dr. G. H. Lunge, Dr. T. F. Rutter and Dr. W. Sachs.

BRITISH STANDARDS INSTITUTION.

The following drafts of British Standards Specifications have been received for technical comment :

CM(LBC)3293, Draft B.S. for Weighing vessels for microchemical analysis.
CM(LBC)3292, Draft B.S. for Crucibles for microchemical analysis.
CM(LBC)3291, Draft B.S. for Combustion boats and sheaths for microchemical analysis.

These have been placed in the Library, and Fellows wishing to make technical comment are requested to do so before September 11th, 1950, to the British Standards Institution, 24/28, Victoria Street, London, S.W.1.

LIST OF APPLICATIONS FOR FELLOWSHIP

(Fellows wishing to lodge objection to the election of these candidates should communicate with the Honorary Secretaries within ten days of the date of publication of the Journal *for August, 1930. Such objections will be treated as confidential. The forms of application are available in the Library.)*

***Ali, Mohamed Ibrahim,** B.Sc. (Fouad 1st Univ.). Egyptian. Fouad 1st University, Faculty of Science, Chemistry Department, Giza, Cairo, Egypt. Demonstrator. *Signed by:* H. A. Fahim, F. G. Baddar, A. Riad Tourky.

Badcock, George Gerald, B.Sc. and Ph.D. (L'pool). British. 417, Cleveland Street, Birkenhead. Fellow of Liverpool University. *Signed by:* W. B. Whalley, J. Mackenzie, N. Walker.

***Bates, Trevor Hugh,** B.Sc. (Birm.). British. 19, Hazel Drive, Dundee. National Service. *Signed by:* L. L. Bircumshaw, S. R. Carter, M. Stacey, F. M. Tayler.

***Beech, Sydney George,** B.Sc. (Birm.). British. 32, Cremorne Road, Four Oaks, Sutton Coldfield, Birmingham. Student at Birmingham University. *Signed by:* L. L. Bircumshaw, M. Stacey, W. Wilson.

***Bearland, Mary Patricia Valerie,** B.Sc. (Bristol). British. Oak Cottage, New Road, Ide Hill, Sevenoaks. Research Student, Bristol University. *Signed by:* F. H. Pollard, John F. W. McOmie, W. Baker.

Champion, John Hardwick Long, B.Sc. (Bristol). British. 27, Woodman's Road, Chipping Sodbury, Bristol. Teacher of Chemistry. *Signed by:* J. K. N. Jones, F. H. Pollard, Leslie Hough.

Chaudhry, Mushtaq Ahmad, B.Sc. and M.Sc.Tech. (Pakistan). Pakistani. 46, Woodlands Drive, Loughborough. Post-graduate Research Scholar, Loughborough College. *Signed by:* R. F. Phillips, J. M. Connolly, G. Oldham, H. K. Suttle.

***Cosgrove, John Derek,** B.Sc. (Dunelm). British. c/o 37, Weardale Crescent, Billingham. Assistant Technical Officer, I.C.I. Ltd. *Signed by:* F. G. Angell, B. W. Bradford, H. N. Wilson.

***Counsell, John Newton.** British. 21, Beechdale Road, Newport. Student. *Signed by:* Leslie Hough, J. K. N. Jones, W. D. Ollis.

Crowder, Frank, A.M.C.T., A.R.I.C. British. 11570, c/o A.I.O.C., Abadan, Iran. Development Chemist. *Signed by:* M. H. Silk, W. A. S. Barbour, J. N. Watson.

Davies, Drury Norman, B.Sc. (Birm.), A.R.I.C., A.M.I.Chem.E. British. Marlowe, Tite Hill, Englefield Green. Sales Manager. *Signed by:* J. J. P. Staudinger, J. J. Wilson, C. E. Hollis.

***Dowling, Lionel Thomas.** British. 16, Mount Avenue, Ealing, W.5. Student, Acton Technical College. *Signed by:* W. Davey, S. C. Bevan, J. W. Spence.

***Dunlop, Lennox Rutherford,** A.R.I.C. British. 16, Primrose Street, Alloa. Analytical Chemist, National Coal Board. *Signed by:* Hugh B. Nisbet, Hugh H. Campbell, J. W. Ingham.

Edgar, Owen Burchell, B.Sc. (Lond.), A.R.C.S. British. 152, Dane Road, Sale, Manchester. Research Chemist, I.C.I. Ltd. *Signed by:* R. J. W. Reynolds, J. D. Rose, W. H. Davies.

Elela, Zeinab Abu, B.Pharm. (Fouad Univ.), Ph.D. (Lond.). Egyptian. School of Pharmacy, Faculty of Medicine, Farouk University, Alexandria, Egypt. Lecturer in Chemistry. *Signed by:* Wilfred H. Linnell, Roy A. Webb, A. S. Shoukry.

***Gilbert, Benjamin,** B.Sc. (Bristol). British. 2, Foxgrove Gardens, Felixstowe. Student, University of Bristol. *Signed by:* W. D. Ollis, D. Easterby, R. Hemming.

***Hampson, Noel Arthur,** B.Sc. (Lond.), A.R.I.C. British. Rainsough Post Office, Prestwich, Manchester. Student at the Royal Technical College, Salford. *Signed by:* E. Whalley, G. Beswick, E. G. Edwards.

Hough, Cyril David, A.R.I.C. British. P.O. Box 138, Lusaka, N. Rhodesia. Chemist, Health Department, N. Rhodesia Government. *Signed by:* J. R. Rowlands, J. W. Gailer, E. Tittensor.

Hutchings, Donald William, B.Sc. (Lond.). British. Scarborough College, Yorkshire. Senior Chemistry Master. *Signed by:* P. F. Onyon, J. Watson, W. G. Barb.

***Jeffries, Edward Arnould Norman Stanley,** B.A. (Oxon.). Canadian. 17, Woodlands Gate, Oakhill Road, Putney, S.W.15. Student. *Signed by:* R. F. Barrow, A. D. Caunt, C. N. Hinshelwood.

***Kempson, Irene Violet Rose.** British. 30, Orford Road, Walthamstow, E.17. Librarian, A. Boake Roberts & Co., Ltd. *Signed by:* Michael F. Carroll, B. Dudley Sully, R. G. Mason.

***Morling, Brian.** British. 5, Ranelagh Gardens, Ilford. Student. *Signed by:* J. Ratcliffe, D. Ridge, Leslie W. King.

Moualim, Richard Joseph, Ph.D. (Bombay and Leeds), A.R.I.C. British. 5, Staverton Road, Willesden Green, N.W.2. Research Chemist, The British Drug Houses, Ltd. *Signed by:* V. Petrow, O. Stephenson, James Forrest.

***Phillips, Kenneth George.** British. 22, Melton Gardens, Romford. Student. *Signed by:* J. Ratcliffe, D. Ridge, M. A. Phillips.

***Popiel, Jan Michal,** B.Sc. (Lond.). Polish. 167, Fordwych Road, London, N.W.2. Student. *Signed by:* Arthur I. Vogel, G. H. Jeffery, J. Leicester.

***Redden, James,** A.R.I.C. British. 2, Tiendhill Green, Duns. Assistant Technical Officer, I.C.I. Ltd. *Signed by:* A. Mackie, Hugh B. Nisbet, Robert G. M. Dakers.

Shen, Tsung-Ying, B.Sc. (Nanking), D.I.C. Chinese. c/o Chemistry Department, The University, Manchester, 13. Research Student. *Signed by:* M. C. Whiting, F. Long, G. R. Barker.

***Stevens, Roger,** B.Sc. (Dunelm). British. 14, Bateman's Acre S., Coundon, Coventry. Post graduate research, King's College, University of Durham. *Signed by:* Ernest E. Tallis, D. Entwistle, E. H. Cole.

***Stuart, Robert Guy,** B.Sc. (Lond.), F.R.I.C. British. **12**, Glanville Drive, Hornchurch. Development Research Chemist. *Signed by:* R. G. Atkinson, N. H. Philip, Charles Simons.

***Torry, Lucie Pauline,** B.Sc. (Lond.). British. **29**, Elm Close, Amersham. Assistant Chemist, D. R. Collins, Ltd., Amersham. *Signed by:* Henry Bowyer, Hector W. Hibbott, Ernest Brown.

***Turner, Alan Herbert.** British. **67**, Ashley Road, Altrincham. Chemistry Student, Oxford University. *Signed by:* L. E. Sutton, J. A. Barltrop, K. J. Morgan.

Vickers, Ernest Edgar. British. **5**, Dickens Road, Grantham. Student, University of Birmingham. *Signed by:* L. L. Bircumshaw, B. H. Newman, M. Stacey.

Warhurst, Ernest, M.Sc. and Ph.D. (Manc.). British. Chemistry Department, The University, Manchester, **13**. Lecturer in Chemistry. *Signed by:* G. R. Barker, T. H. H. Quibell, H. A. Skinner.

Wood, Leslie James, B.Sc. and Ph.D. (Lond.), F.R.I.C. British. **4**, Hollin View, Leeds, **6**. Research Chemist, The Coal Tar Research Association. *Signed by:* Donald McNeil, Felix Popper, E. N. White.

***Zimmerman, Aaron Arnold,** B.Sc. (Lond.). British. **183**, Brady Street Buildings, Whitechapel, E.1. Scientific Civil Servant. *Signed by:* J. H. Wood, S. Kaminsky, L. D. Huckstepp.

UNDER SPECIAL PROVISION APPERTAINING TO CANDIDATES RESIDENT ABROAD.

Calvin, Melvin, B.S. (Michigan Coll. of Tech.), Ph.D. (Minnesota). American. Department of Chemistry, University of California, Berkeley, California. Professor of Chemistry. *Signed by:* M. G. Evans.

Dodson, jun., Vance Hayden, B.Ch.E. and M.S. (Toledo). American. Department of Chemistry, Purdue University, Lafayette, Indiana. Graduate Student and Assistant. *Signed by:* Nathan Kornblum.

Graydon, William Frederick, M.A.Sc. (Toronto), Ph.D. (Minnesota). Canadian. Department of Chemical Engineering, University of Toronto, Toronto, Ontario. Assistant Professor. *Signed by:* D. W. H. MacDowell, R. B. McLaughlin.

Herbert, jun., Stephen Aven, M.S. (Penn. State College). American. Department of Chemistry, Purdue University, Lafayette, Indiana. Graduate Student and Research Fellow. *Signed by:* Nathan Kornblum.

Herbrandson, Harry Fred, B.Chem. (Minnesota), Ph.D. (Ill.). American. Walker Laboratory, Rensselaer Polytechnic Institute, Troy, New York. Assistant Professor of Organic Chemistry. *Signed by:* George J. Janz.

Kamal, Ahmad, M.Sc. (Alig.), Ph.D. (L'pool). Pakistani. Institute of Chemistry, Punjab University, Mall, Lahore, Pakistan. Senior Lecturer in Organic Chemistry. *Signed by:* M. I. D. Chughtai.

King, Lafayette Carroll, Ph.D. (Michigan). American. Department of Chemistry, Northwestern University, Evanston, Illinois. Associate Professor of Chemistry. *Signed by:* Frederick G. Bordwell, Ludwig Bauer.

Kosak, Alvin Ira, B.S. (Coll. of New York), Ph.D. (Ohio State). American. Department of Chemistry, University of Cincinnati, Cincinnati **21**, Ohio. Assistant Professor of Chemistry. *Signed by:* Christopher L. Wilson.

Leisegang, Ernest Cecil, M.Sc. (S.A.). South African. Flat **37**, Oribi, Pietermaritzburg, South Africa. Lecturer in Inorganic Chemistry. *Signed by:* F. L. Warren, H. A. E. Mackenzie.

***Meinwald, Jerrold,** Ph.B. (Chicago), A.M. (Harvard). American. Converse Laboratories, **108**, Department of Chemistry, Harvard University, Cambridge **38**, Massachusetts. Student and Teaching Fellow in Chemistry. *Signed by:* Frans Sondheimer.

***Ramakrishnan, C. V.,** M.Sc. and Ph.D. Indian. Department of Biochemistry, Indian Institute of Science, Bangalore **3**, India. Fellow of The Indian Council of Medical Research. *Signed by:* S. S. Bhatnagar.

Stickler, William Carl, A.B., A.M., and Ph.D. (Columbia Univ.). German. Department of Chemistry, University of Denver, Denver **10**, Colorado, U.S.A. Assistant Professor of Chemistry. *Signed by:* W. Doering.

***Wilkinson, Leslie Ronald,** M.Sc. (Melbourne). Australian. 21, Geddes Street, Ascot Vale, W.2, Victoria, Australia. Research Chemist, Monsanto Chemicals (Australia), Ltd. *Signed by:* W. Davies, Stewart F. Cox.

* Reduced annual subscription.

PAPERS RECEIVED

(List of papers received between June 13th and July 31st, 1950.)

"Substituted anthracene derivatives. Part IV. The ultra-violet absorption spectra of *meso*-substituted 1 : 2-benzanthracenes." By G. M. BADGER and R. S. PEARCE.

"2- and 4-Nitro-3-aminocarbazole." By GEORGE ANDERSON and NEIL CAMPBELL.

"Contribution to the study of the chemical and physical properties of ethanol–water mixtures." By M. Bobtelsky.

"The heat of solution of halogenides, sulphuric acid, oxalic acid, sodium hydroxide, and urea in ethyl alcohol–water mixtures." By M. Bobtelsky and R. D. Larisch.

"Absorption spectra and structure of organic sulphur compounds. Part VII. Sulphoxides." By H. P. Koch.

"Pyrazine derivatives. Part XII. Sulphanilyl derivatives of 2-amino-3 : 6-di-*sec.*-butylpyrazine." By G. T. Newbold.

"Some chroman and 1 : 2-benzopyran derivatives." By Helan V. Taylor and Muriel L. Tomlinson.

"Organosilicon compounds. Part II. A 'conversion series' for organosilicon halides, pseudohalides, and sulphides." By C. Eaborn.

"Mercurous nitrate as a reductometric reagent. Part I. Stoicheiometry of the reaction." By R. Belcher and T. S. West.

"Mercurous nitrate as a reductometric reagent. Part II. The interference of the more common cations and anions in the determination of iron." By R. Belcher and T. S. West.

"Mercurous nitrate as a reductometric reagent. Part III. The titration of various oxidising agents." By R. Belcher and T. S. West.

"Mercurous nitrate as a reductometric reagent. Part IV. The determination of copper." By R. Belcher and T. S. West.

"The action of ionizing radiations and of radiomimetic chemicals on deoxyribonucleic acid. Part II. The effect of oxygen on the degradation of the nucleic acid by *X*-rays." By J. A. V. Butler and B. E. Conway.

"Synthesis of potential antibacterial agents. Part I. Some α-alkylglutaric acids and their derivatives." By John C. Roberts and Bernard Shaw.

"The dipole moments of ethylene oxide and carbonyl chloride in benzene solution, and a note on a useful modification of the Barclay–Le Fèvre equation." By C. L. Angyal, G. A. Barclay, and R. J. W. Le Fèvre.

"The electrochemical behaviour of the antimony electrode." By S. E. S. ElWakkad.

"The synthesis of long-chain aliphatic acid from acetylenic compounds. Part IV. A new approach to the synthesis of branched-chain acids." By C. L. Leese and R. A. Raphael.

"Intramolecular acylation. Part II. The ring closure of some α-substituted glutaric acids." By M. F. Ansell and D. H. Hey.

"An unambiguous synthesis of 3-aroylflavones and their reaction with benzylamine." By Wilson Baker and F. Glockling.

"Steroids and related compounds. Part X. The preparation of pregna-5 : 17-diene-3β : 21-diol." By D. Magrath, D. S. Morris, V. Petrow, and R. Royer.

"*trans*-8 : 9-Epoxy-11-ketoheptadecane-1-carboxylic acid and *cis*-10 : 11-diketoheptadec-8-ene-1-carboxylic acid, with some observations on the ultra-violet absorption spectra of these and related compounds." By George King.

"The degradation of α-amino-acids by interaction with aldehydes." By Radwan Moubasher.

"The condensed phosphoric acids and their salts. Part V. Dissociation constants of some tetrametaphosphates." By H. W. Jones and C. B. Monk.

"Fluorescence quenching by colloid anions and cations." By J. E. Lovelock.

"The seed fat of *Macadamia ternifolia*." By R. E. Bridge and T. P. Hilditch.

"Organic fluorides. Part V. Fluorination of hydrocarbons with cobalt trifluoride." By R. N. Haszeldine and F. Smith.

"The state of dissolved sulphur dioxide in sulphuric acid." By V. Gold and F. L. Tye.

"The condensation of aromatic amines with formylchloroacetic ester." By D. A. H. Taylor.

"The optical resolution of (±)-*trans*-9 : 10-dihydroxy-9 : 10-dihydrophenanthrene." By J. Booth, E. Boyland, and E. E. Turner.

"Cryoscopic studies in sulphuric acid. Part VIII. The solutes acetic anhydride and benzoic anhydride. Cryoscopic evidence for the acetylium and benzoylium ions." By R. J. GILLESPIE.

"The *Euphorbia* resins. Part V. Oxidative degradation in the side chain of euphol." By HS. K. KRÜSI.

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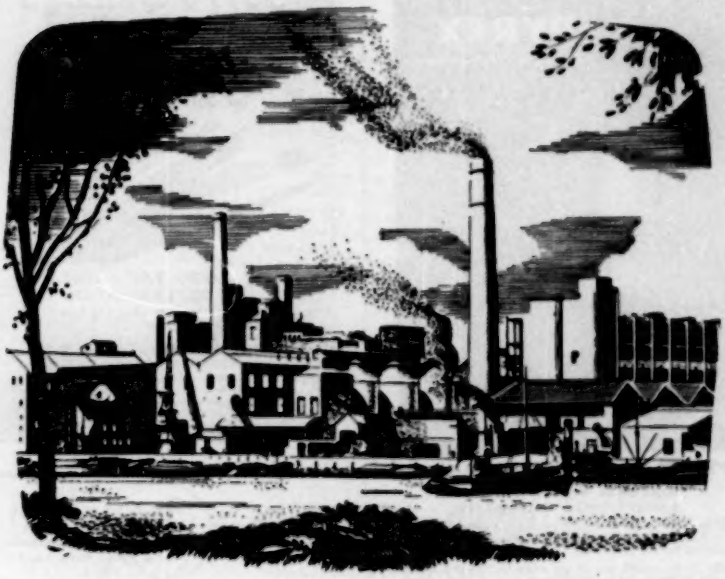

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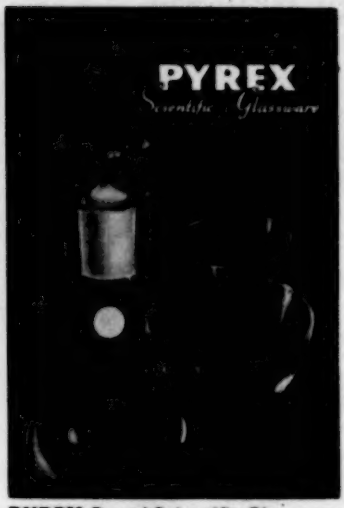

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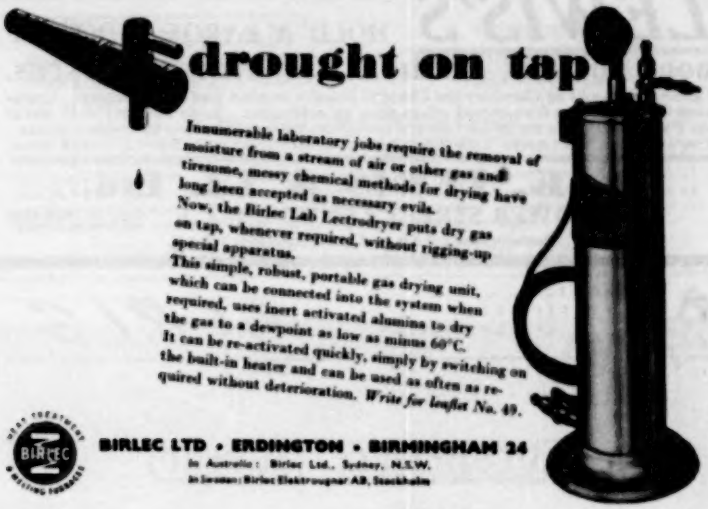

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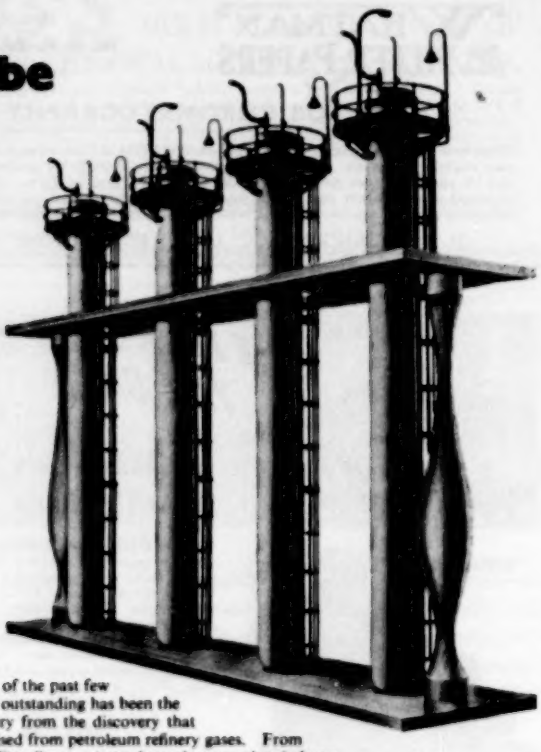

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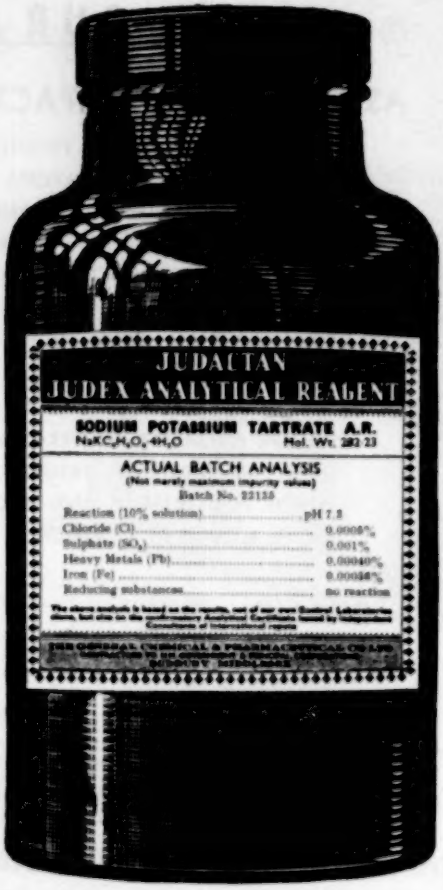

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403. *Alkali Organometal Compounds. Part I. The Reaction of Benzylsodium with Alkyl Halides.*

By D. Bryce-Smith and E. E. Turner.

A simple method for the preparation of pure alkylbenzenes is described, based on the reaction between benzylsodium and alkyl halides.

Modification of a previously described method for the preparation of benzylsodium has made it possible to obtain improved yields of alkylbenzenes by the reaction. Yields are higher than in the corresponding reaction using phenylsodium.

p-Xylene has been prepared by the interaction of *p*-tolylsodium with methyl iodide and methyl sulphate.

Refractive indices, densities, and boiling points have been determined for a number of pure alkylbenzenes.

Morton and his co-workers (*J. Amer. Chem. Soc.*, 1938, **60**, 1429; 1941, **63**, 327) prepared *n*-amylbenzene by the reaction sequence

$$n\text{-}C_5H_{11}Cl \xrightarrow[\text{benzene}]{\text{Na in}} C_6H_5Na \xrightarrow{\text{toluene}} C_6H_5\cdot CH_2Na \xrightarrow{n\text{-}C_5H_{11}Cl} C_6H_5\cdot C_5H_{11}$$

The reaction of *n*-alkyl chlorides with sodium in toluene was also shown to produce *n*-alkylbenzenes through the intermediate formation of benzylsodium.

A similar method has been used by Letsinger (*ibid.*, 1948, **70**, 406) to prepare optically active alkylbenzenes by the interaction of benzylsodium with (+)-2-bromobutane and (+)-2-bromooctane. *n*-Butyl and *n*-amyl chlorides were used for the preparation of benzylsodium, the yield being low in the former case.

As part of a programme of work on the preparation of pure hydrocarbons, we have studied the reaction of benzylsodium with a number of aliphatic halides. Benzylsodium prepared from *n*-amyl chloride as described by the above workers was considered unsuitable for the preparation of the lower alkylbenzenes in a pure state owing to the difficulty of complete separation from decane.

Gilman, Pacevitz, and Baine (*ibid.*, 1940, **62**, 1514) claimed to have obtained a 79% yield of benzylsodium, estimated as phenylacetic acid, by the interaction of chlorobenzene and sodium in toluene at 35°; the toluene suspension of phenylsodium obtained, heated under reflux for 3 hours, gave benzylsodium:

$$C_6H_5Na + C_6H_5\cdot CH_3 \longrightarrow C_6H_6 + C_6H_5\cdot CH_2Na$$

These have been reported as optimum conditions (Pacevitz, *J. Iowa State Coll. Acad. Sci.*, 1941, **16**, 117).

Using benzylsodium prepared by this method, we have obtained moderate yields of alkylbenzenes by interaction with primary and secondary halides. However, it has been found that the heating period of 3 hours for the preparation of benzylsodium is excessive, the reaction being, in fact, complete within 35 minutes at 105°. Moreover, in reactions with alkyl halides, benzylsodium prepared with the shorter heating period has given yields of alkylbenzenes approximately 15% higher, together with correspondingly decreased formation of tarry by-products. Reduction in the amount of toluene to half that used by Gilman *et al.* (*loc. cit.*) has not decreased yields.

We conclude that slow thermal decomposition of benzylsodium occurs at 105°.

Other experiments on the metallation of toluene have shown that approximately 25% formation of benzylsodium occurs when the suspension of phenylsodium in toluene is kept at room temperature for 20 hours. At 80°, conversion is almost complete after 1 hour.

Experiments with *n*-butyl halides have shown that temperature is an important factor in their reaction with benzylsodium. With the chloride and iodide, the highest yields of *n*-amylbenzene were obtained at 30°, whereas with the bromide the reaction was best performed at 105°. Approximately equal yields were obtained in each case. From the experimental point of view, the use of bromides was most convenient.

Secondary halides have likewise given good yields of the coupled product with benzylsodium.

tert.-Butyl halides have given very small yields of phenyl*neo*pentane, not increased by working at −75°.

Normal coupling products have been obtained in good yields from allyl chloride and *cyclo*hexyl bromide. In the former case 4-phenylbut-1-ene was obtained free from isomeric unsaturated hydrocarbons.

For purposes of comparison, the reaction of ethyl and *n*-butyl bromides with phenylsodium has been examined. Yields of the coupled product have been found to be lower than in corresponding reactions using benzylsodium. This is in agreement with the observations of Morton (*loc. cit.*).

n-Butylbenzene prepared from phenylsodium has been found to be identical in physical properties with that prepared from benzylsodium. This excludes the possibilities of isomerisation or an *ortho*-reaction with benzylsodium.

Since benzylsodium is known to form ethylbenzene by its interaction with methyl sulphate (Morton, *J. Amer. Chem. Soc.*, 1940, **62**, 120) the reaction of phenylsodium with toluene-*p*-sulphonic esters was thought likely to prove an alternative route to alkylbenzenes. However, interaction of phenylsodium and *n*-butyl toluene-*p*-sulphonate gave a low yield of octane and no trace of the expected *n*-butylbenzene.

Reactions with p-*Tolylsodium.*—*p*-Tolylsodium is known to form benzylsodium slowly on long standing at room temperature (Bachmann and Clarke, *ibid.*, 1927, **49**, 2089) and more rapidly on heating (Gilman and Pacevitz, *ibid.*, 1940, **62**, 673). We have confirmed the latter authors' observation that interaction of *p*-chlorotoluene and sodium, followed immediately by treatment of the product with carbon dioxide, gives pure *p*-toluic acid and no phenylacetic acid.

By the interaction of *p*-tolylsodium and methyl iodide or methyl sulphate, *p*-xylene has been prepared in moderate yields. The yield of *p*-xylene from methyl sulphate was higher than the yield of *p*-toluic acid obtained from the reaction with carbon dioxide. This is of interest in view of the frequent use of the latter reaction for the estimation of organo-sodium compounds.

The absence of isomerisation and unsaturated by-products has made the reaction of these organo-sodium compounds with aliphatic halides very convenient for the preparation of pure alkylbenzenes. In the conditions used, the symmetrical Wurtz coupling product is formed in traces insufficient for its isolation and in most cases the required alkylbenzenes have been readily obtained pure by straightforward fractional distillation.

However, 2—3% of diphenyl is formed in the initial preparation of phenylsodium and, in the case of alkylbenzenes with a boiling point near to that of diphenyl, careful fractionation has been necessary in order to obtain pure products. The presence of traces of diphenyl is easily detected by refractive-index measurements.

Measurements of boiling points, refractive indices, and densities for hydrocarbons obtained in this work are recorded in Table II. The values have been found to be highly reproducible despite the fact that preparations have been on the relatively small scale of 0·5 g.-mol.

Where comparison is possible, the values are in close agreement with those obtained by Forziati, Norris, and Rossini (*J. Res. Nat. Bur. Stand.*, 1949, **43**, 473, 555) working with a series of specially purified hydrocarbons.

Agreement with the values give by Vogel (*J.*, 1948, 607) is less consistent.

Further work on the physical properties of alkylbenzenes is in progress and will be reported in a later paper.

Experimental.

(All temperatures are corrected.)

Alkyl bromides were prepared from the corresponding refractionated alcohols by standard methods. Other halides were commercial products purified by shaking them with concentrated sulphuric acid, washing, drying, and distillation. All halides were refractionated before use, through a jacketed Fenske column with 35-cm. packed length and variable take-off (column A).

Benzene and toluene were sulphur-free. Light petroleum was freed from aromatic and unsaturated compounds by being shaken with 5% oleum, washed, dried, and distilled. All reagents were carefully dried.

The experimental conditions are illustrated by the following preparation of *n*-butylbenzene (any deviation is indicated in the notes to Table I).

A 1-l. flask was fitted with a dropping funnel, reflux condenser, wing-stirrer with mercury seal, thermometer, and gas inlet, all joints being of ground glass. In the flask were placed 300 c.c. of toluene and 27·5 g. (1·2 g.-at.) of sodium wire. The apparatus was filled with dry nitrogen and stoppered. At 30—35°, 64 g. (0·6 g.-mol.) of chlorobenzene were added dropwise during 2 hours, with vigorous stirring. Reaction started within a few minutes, the sodium surface becoming black, and was complete after a further 1½—2 hours at 30°.

The condenser was then fitted with a calcium chloride tube, and the mixture heated under reflux with stirring for 35 minutes. The reflux temperature, initially 107°, soon fell to 103° as benzene became formed by the exchange reaction. After removal of the heating bath, 49 g. (0·4 g.-mol.) of *n*-propyl bromide were added during 20 minutes at 103—105°.

After the mixture had cooled to room temperature, an excess of solid carbon dioxide was added to show the presence of unchanged benzylsodium. Water was finally added to destroy excess of sodium. The separated and dried toluene layer was distilled through column (A). No fraction corresponding to *n*-hexane was observed. After removal of most of the toluene through this column, the latter was replaced by a smaller one (B) of the same type with 8-cm. packed length.

The following fractions were collected at 765 mm. :

No.	B. p.	n_D^{20}.	Wt., g.	No.	B. p.	n_D^{20}.	Wt., g.
(1)	111—145°	1·4920		(8)	181·5°	1·4903	2
(2)	145—170	1·4915	3	(9)	181·5—247	—	1·5
(3)	170—181·0	1·4901	4·5	(10)	247—275	—	1·5
(4)	181·0	1·4898		(11)	275—295	—	1·0
(5)	181·0—181·5	1·4898	35·5		Residue	—	6·5
(6)	181·5	1·4898					
(7)	181·5	1·4898					

Redistillation of (3) and (8) gave a further 4·5 g. of *n*-butylbenzene, b. p. 181·0—181·5°/765 mm., n_D^{20} 1·4898. [At these rather high temperatures, a thermometer immersed in the vapour at the top of a fractionating column rarely records the true b. p. For this reason, refractive indices rather than b. p.s have been taken as criteria of purity. More accurate values for b. p.s have been obtained by using the Spencer–Cottrell apparatus (Table II).]

The total yield of pure *n*-butylbenzene was 40 g. (74%).

Acidification of the aqueous layer gave 3·9 g. of crude phenylacetic acid, m. p. 67—69°. Crystallisation from water gave 2·4 g. of m. p. 77°.

TABLE I.

Yields of alkylbenzenes from the interaction of benzylsodium with halides.

Yields of pure products (%; calculated on halides) from 0·6 g.-mol. of chlorobenzene, 1·2 g.-at. of sodium, and 0·4 g.-mol. of alkyl halides.

	Reaction temp.[a]				Reaction temp.[b]		
Alkyl halide.	−70°.	30°.	70°.	105°.	30°.	105°.	Product.
Ethyl bromide	—	—	—	50	—	—	*n*-Propylbenzene
n-Propyl bromide	—	—	—	57[c]; 60[d]	—	76; 74[d]	*n*-Butylbenzene
n-Butyl chloride	—	62	48	39	—	—	*n*-Amylbenzene
n-Butyl bromide	—	55[c]; 54	—	67	—	79; 80[b]	*n*-Amylbenzene
n-Butyl iodide	—	65	—	60	—	—	*n*-Amylbenzene
n-Amyl bromide	—	—	—	—	—	73	*n*-Hexylbenzene
1-Bromo-3 : 5 : 5-trimethylhexane	—	—	—	55[f]	—	—	1-*Phenyl*-4 : 6 : 6-*trimethylheptane*
*iso*Propyl bromide	—	—	—	51	—	—	*iso*Butylbenzene
sec.-Butyl bromide	—	52	—	55	—	70[d]	1-Phenyl-2-methylbutane
sec.-Butyl chloride	—	—	—	—	72[b]	—	1-Phenyl-2-methylbutane
tert.-Butyl chloride	—	1·5	—	1·5[f]	—	—	Phenyl*iso*pentane
tert.-Butyl bromide	1·0	2·5	—	—	—	—	Phenyl*iso*pentane
*cyclo*Hexyl bromide	—	—	—	—	—	69[c,b]	*cyclo*Hexylphenylmethane
Allyl chloride	—	51	—	—	72[d]	—	4-Phenylbut-1-ene

[a] Benzylsodium prepared by heating phenylsodium in toluene for 3 hrs. at 105° (Gilman *et al.*, *loc. cit.*). [b] Benzylsodium prepared by heating phenylsodium in toluene for 35 mins. at 105°. [c] Sodium powder was used instead of sodium wire in this experiment. Reaction with chlorobenzene was more difficult to initiate and proceeded more slowly. [d] Solid carbon dioxide was added to the reaction mixture before addition of water. Phenylacetic acid was obtained in each case. [e] 0·5 G.-mol. of *n*-butyl bromide used. [f] Owing to the proximity of the b. p. of 1-phenyl-4 : 6 : 6-trimethylheptane to that of diphenyl, there was considerable distillation loss on working up and the true yield was much higher. B. p. 96°/2·5 mm. (Found : C, 88·2; H, 11·9. $C_{16}H_{26}$ requires C, 88·0; H, 12·0%). [g] *cyclo*Hexylphenylmethane was not obtained in a state of purity comparable with that of the other hydrocarbons in this series. Practically all of the product distilled at 130·0—130·5°/20 mm. and showed no unsaturation to bromine in carbon tetrachloride; n_D^{20} 1·5245—1·5270. After being heated at 130° with sodium for several hours, the hydrocarbon had b. p. 122·5—123·0°/16 mm., n_D^{20} 1·5258—1·5264. These variations in refractive index may have been due to the presence of traces of di*cyclo*hexyl. The p-*sulphonamide* formed colourless crystals (from light petroleum), m. p. 107·5° (Found : N, 5·4. $C_{19}H_{19}O_2NS$ requires N, 5·5%). Sidorova and Tsukervanik (*J. Gen. Chem. Russia*, 1941, **10**, 2073) give for *cyclo*hexylphenylmethane, b. p. 137°/20 mm., n_D^{15} 1·5255. [h] In these experiments the amount of toluene was reduced from 300 c.c. to 150 c.c. (1·4 g.-mols.). The heating period at 100° for complete formation of benzylsodium was 50 mins. These are probably the best experimental conditions. [i] Phenyl*iso*pentane was purified by being heated under reflux for several hours with alkaline permanganate; b. p. 185—186°. The p-*sulphonamide* formed colourless crystals (from light petroleum), m. p. 86° (Found : N, 6·3. $C_{11}H_{17}O_2NS$ requires N, 6·2%).

Metallation of Toluene at Lower Temperatures.—(1) *At 25°.* A suspension of phenylsodium in 300 c.c. of toluene prepared from 0·6 g.-mol. of chlorobenzene and 1·2 g.-atoms of sodium was stirred at 25° for

20 hours. At 30°, 55 g. (0·4 g.-mol.) of *n*-butyl bromide was added during 2 hours and the mixture stirred for 1 hour more. On working up and fractionating the product, 11 g. (19%) of *n*-amylbenzene were obtained, indicating approximately 25% formation of benzylsodium.

(2) *At 80°.* A suspension of phenylsodium in 300 c.c. of toluene was prepared from 0·6 g.-mol. of chlorobenzene and 1·2 g.-atoms of sodium and heated at 80° for 1 hour. 49 G. (0·4 g.-mol.) of *n*-propyl bromide was run in at 80° during 20 minutes and on cooling to room temperature, *ca.* 50 g. of solid carbon dioxide were added to the mixture. Water was added and, on distillation of the organic layer, no fraction corresponded to *n*-propylbenzene. However, it was not possible to obtain the normal sharp fraction corresponding to *n*-butylbenzene, the hydrocarbon obtained having a b. p. range of 178—181°/764 mm. and n_D^{19} 1·4884—1·4889 (35·5 g.).

Acidification of the aqueous liquor gave 1·5 g. of acids, m. p. 70—90°.

It was concluded that, under these conditions, the formation of benzylsodium was incomplete.

Experiments with Phenylsodium.—Reaction with n-butyl bromide. Phenylsodium was prepared from 27·5 g. (1·2 g.-atoms) of sodium wire and 68 g. (0·6 g.-mol.) of chlorobenzene in 300 c.c. of benzene under the conditions used previously with toluene as solvent. At 30°, 55 g. (0·4 g.-mol.) of *n*-butyl bromide were added during 2 hours with stirring. After a further hour at 30° water was added to decompose excess of sodium and phenylsodium. Distillation of the organic layer gave 30 g. (56%) of crude *n*-butylbenzene, b. p. 179—182°/751 mm., n_D^{20} 1·4903, slightly unsaturated to bromine in carbon tetrachloride.

After heating of the crude product under reflux with sodium for 2 hours and refractionation (column B), 23·5 g. (44%) of *n*-butylbenzene were obtained, having b. p. 180—181°/751 mm., n_D^{20} 1·4898, and saturated to bromine in carbon tetrachloride, and also 4·7 g. (7·5%) of diphenyl, m. p. 70°. This was the only experiment in which the formation of unsaturated matter was observed.

To find the effect of reaction temperature on the yield of *n*-butylbenzene, an experiment similar to the above was carried out with light petroleum (b. p. 100—120°) as solvent, addition of *n*-butyl bromide being made at 105° during 20 minutes. The yield of pure *n*-butylbenzene was 26·5 g. (49%).

Reaction with ethyl bromide. See also Acree (*Amer. Chem. J.*, 1903, **29**, 588). This experiment was carried out to check varying literature values for the refractive index of ethylbenzene.

A suspension of phenylsodium was prepared from 46 g. (2 g.-atoms) of sodium wire and 112·5 g. (1 g.-mol.) of chlorobenzene in 400 c.c. of light petroleum (b. p. 40—60°). 87 G. (0·8 g.-mol.) of ethyl bromide were added at 30° during 45 minutes and the mixture was stirred a further hour. Addition of water and normal working-up gave 42·5 g. (50%) of ethylbenzene showing no unsaturation with bromine in carbon tetrachloride and having n_D^{20} 1·4958. The hydrocarbon, heated under reflux with sodium for 8 hours and refractionated (column A), had b. p. 134·4°/745 mm. and n_D^{20} 1·4958.

Reaction with n-butyl toluene-p-sulphonate. To a suspension of phenylsodium prepared from 34 g. (0·3 g.-mol.) of chlorobenzene and 13·8 g. (0·6 g.-atom) of sodium wire in 150 c.c. of benzene were added 45·5 g. (0·2 g.-mol.) of freshly-distilled *n*-butyl toluene-*p*-sulphonate during 45 minutes at 50°. After the mixture had been kept overnight at room temperature, water was added and the separated organic layer fractionated. 1 G. of a liquid, b. p. 125—131°, was obtained, which was saturated to bromine in carbon tetrachloride, had n_D^{20} 1·4140, and was thus probably *n*-octane.

No fraction corresponding to *n*-butyl benzene was observed.

Experiments with p-Tolylsodium.—Reaction with carbon dioxide. (Cf. Gilman and his co-workers, *J. Amer. Chem. Soc.*, 1940, **62**, 673, 1514.) *p*-Tolylsodium was prepared by addition of 12·6 g. (0·1 g.-mol.) of *p*-chlorotoluene during 2 hours to 4·6 g. (0·2 g.-atom) of sodium wire stirred in 50 c.c. of light petroleum (b. p. 40—50°) at 25° with the usual conditions for exclusion of air and moisture. The mixture was stirred for a further 2 hours at 25° and then rapidly poured on a large excess of solid carbon dioxide in a Dewar flask. Next morning water was added to destroy excess of sodium. Acidification of the aqueous layer gave 6·8 g. of *p*-toluic acid, almost pure without recrystallisation, m. p. 175°. Ether-extraction of the mother-liquor gave 0·15 g. of a brown acid, m. p. 161—163° without recrystallisation. From the odour, this contained traces of cresol. Phenylacetic acid was not found. The yield of *p*-toluic acid was 51%.

Reaction with methyl iodide. *p*-Tolylsodium was prepared, as in the previous experiment, from 50·5 g. (0·4 g.-mol.) of *p*-chlorotoluene and 23 g. (1 g.-atom) of sodium wire in 200 c.c. of light petroleum (b. p. 30—40°). 51 G. (0·36 g.-mol.) of methyl iodide were added at 30° during 30 minutes. Reaction was rapid. After a further 5 minutes' stirring, solid carbon dioxide was added to decolorise the solution. Excess of sodium was destroyed by addition of water. Fractionation at 745 mm. (column A) gave the following fractions:

No.	B. p.	Wt., g.	M. p.	No.	B. p.	Wt., g.	M. p.
(1)	90—120°	1·0	<0°	(5)	136·0—136·5°	1·9	12·0—12·3°
(2)	120—132	1·5	<0	(6)	136·5	14·2	12·3—12·7
(3)	132—135	1·0	<0		Residue	3	—
(4)	135—136	1·3	8·5—9·0				

Fractions (5) and (6) represent a 42% yield of *p*-xylene. Fraction (6) had n_D^{20} 1·49584.

The aqueous layer gave, on acidification, 2·85 g. (5·2%) of *p*-toluic acid, m. p. 175—176°, without recrystallisation.

Reaction with methyl sulphate. *p*-Tolylsodium was prepared, as in previous experiments, from 76 g. (0·6 g.-mol.) of *p*-chlorotoluene and 27·5 g. (1·2 g.-atoms) of sodium wire in 250 c.c. of light petroleum (b. p. 40—50°). At 30°, a mixture of 78·5 g. (0·625 g.-mol.) of methyl sulphate with 30 c.c. of

benzene was added during 1 hour with vigorous stirring. The reaction mixture was then colourless. After addition of water, the organic layer was fractionated until the vapour temperature reached 90°. The crude *p*-xylene was then steam-distilled in the presence of potassium hydroxide. The dried steam-distillate was fractionated (column A) at 773 mm. and the following fractions were collected :

No.	B. p.	Wt., g.	M. p.	No.	B. p.	Wt., g.	M. p.
(1)	109—115°	2·9	<0°	(6)	138·0—138·3°	4·5	11·9—12·1°
(2)	115—132	3·5	<0	(7)	138·3—138·35	12·1	12·1—12·8
(3)	132—136	2·0	<0	(8)	138·35	11·4	12·6—12·8
(4)	136—137	2·4	7·5—8·5		Residue	5·3	—
(5)	137—138	2·5	10·4—10·8				

Distillation of the residue from a small flask without a column gave a further 4·2 g., m. p. 10·0—10·5°, b. p. 138—140° (fraction 9). Fractions (5)—(9) (37·1 g.) represent a 58% yield, based on *p*-chlorotoluene.

Physical Properties.—Data for the purest products obtained are given in Table II.

TABLE II.

	B. p./760 mm.	n_D^{20}.	d_4^{20}.		B. p./760 mm.	n_D^{20}.	d_4^{20}.
Ethylbenzene	136·1°	1·49577	0·86709	4-Phenylbut-1-ene ...	181·1°	1·50748	0·88153
p-Xylene	138·0	1·49579	0·86106	*n*-Amylbenzene	205·2	1·48827	0·85904
n-Propylbenzene.....	159·4	1·49186	0·86200	1-Phenyl-2-methylbutane	196·1	1·48906	0·86072
n-Butylbenzene :							
(i) *ex* $C_6H_5{\cdot}CH_2Na$...	182·9	1·48975	0·86017	*n*-Hexylbenzene.....	225·0	1·48698	0·85830
(ii) *ex* C_6H_5Na	—	1·48974	0·86017	1-Phenyl-4 : 6 : 6-trimethylheptane	—	1·48268	0·85591
*iso*Butylbenzene	172·7	1·48657	0·85345				

Refractive indices were measured with a calibrated Pulfrich refractometer. Reproducibility with this instrument was ±0·00002 and values obtained with different samples came within these limits.

Densities are for the air-saturated hydrocarbons and are reduced to a vacuum. Individual measurements were reproducible within ±0·00003 g./ml.

B. p.s were measured with the Spencer–Cottrell apparatus and were reproducible within ±0·2°.

All measurements were made with hydrocarbons freshly distilled over sodium or potassium. Slight deterioration, probably by oxidation, was observed when samples were kept in stoppered bottles for some months.

We are indebted to Dr. V. C. G. Trew for the measurements of refractive indices and densities recorded herein and also express our thanks for the financial assistance received through the Institute of Petroleum which has made this work possible.

BEDFORD COLLEGE, UNIVERSITY OF LONDON. [*Received, March 31st*, 1950.]

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404. *Reaction-kinetic Investigations of the Incomplete Dissociation of Salts. Part II. The Hydrolysis of Carbethoxymethyltriethylammonium Iodide and of Ethyl Acetate by Solutions of Metal Hydroxides.*

By R. P. BELL and (MRS.) G. M. WAIND.

Kinetic measurements have been made on the alkaline hydrolysis of carbethoxymethyltriethylammonium iodide at 0°. The reaction shows a large primary negative salt effect, and is specifically retarded by calcium and barium ions. This retardation can be accounted for by the formation of $CaOH^+$ and $BaOH^+$, and agrees quantitatively with the dissociation constant of $CaOH^+$ at 0°, which was determined by measuring the solubility of calcium iodate in solutions of sodium hydroxide. Measurements on the alkaline hydrolysis of ethyl acetate showed that calcium and barium ions have no detectable retarding effect in this reaction. The varying behaviour in different reactions involving hydroxyl ions is accounted for in terms of the properties of the transition state.

IN the first paper of this series (Bell and Prue, *J.*, 1949, 362) it was shown that, when diacetone alcohol decomposes in presence of hydroxyl ions, the presence in the solution of calcium, barium, or thallium ions causes a reduction in reaction velocity which can be reasonably accounted for in terms of the incomplete dissociation of the hydroxides concerned. For the hydroxides of barium and thallium the degrees of dissociation agreed with those obtained by other methods (*e.g.*, solubility measurements), but for calcium hydroxide the kinetic value was higher by an amount which probably exceeded the experimental error. It was pointed out that the apparent degrees of dissociation derived from kinetic measurements will be too high if the metallic ions

concerned associate with the transition state of the reaction as well as with the hydroxyl ion. This association with the transition state is likely to be a minimum in a reaction such as

$$^{+}NEt_3{\cdot}CH_2{\cdot}CO_2Et + OH^- \longrightarrow {}^{+}NEt_3{\cdot}CH_2{\cdot}CO_2^- + EtOH$$

where the transition state has a net charge of zero, and we have therefore made measurements of the velocity of this reaction in presence of sodium, calcium, and barium ions. In order to determine the degree of dissociation of $CaOH^+$ at 0°, a study was made of the solubility of calcium iodate in solutions of sodium hydroxide at this temperature, and some kinetic experiments were made on the hydrolysis of ethyl acetate by various hydroxides.

Experimental.

Carbethoxymethyltriethylammonium chloride was prepared by the reaction of equivalent quantities of triethylamine and ethyl monochloroacetate in alcohol at 0°. The crude chloride was dissolved in acetone and treated with one equivalent of potassium iodide; after the potassium chloride had been filtered off, the solution was evaporated to dryness and the iodide recrystallized from acetone, giving fine white crystals, m. p. 126—127°, 99·9% pure by titration with silver nitrate.

Kinetic measurements were carried out at 0° with equal initial concentrations (0·003—0·006M.) of ester salt and sodium hydroxide free from carbonate. In most experiments the solutions also contained sodium chloride, barium chloride, or calcium chloride; the concentrations of the last two substances were determined in their stock solutions by the gravimetric estimation of chloride (as silver chloride) and barium (as barium sulphate), and the volumetric determination of calcium as oxalate.

In making kinetic measurements the solution containing sodium hydroxide and added salt was contained in a small flask, and 1 c.c. of a stock solution of ester (which was stable for at least several days) in a thin-walled glass bulb resting on the bottom of the flask. A slow stream of air freed from carbon dioxide was passed through during the whole experiment. After 20 minutes at 0° the bulb was broken and a clock started simultaneously. After a suitable reaction time (0·5—4 minutes) the reaction was stopped by adding 10 c.c. of N/100-hydrochloric acid, and the excess of acid titrated with N/100-ammonia solution (methyl-red). Six such experiments were carried out with each reaction mixture, using reaction times covering about two-thirds of the total reaction. As a check one experiment in each set was allowed to continue to completion: the observed titres agreed with those calculated, within experimental error.

Because of the short times and high dilutions involved the individual observations are not very accurate. The second-order velocity constants k were obtained by plotting $x/(a - x)$ (a = initial concentration of both reactants, $a - x$ = concentration after time t) against the time in minutes, and determining the slope of the best straight line (ak) by the method of least squares. Fig. 1 shows the lines for two typical reactions. Table I gives the observed velocities for all the solutions studied.

Table I.

Hydrolysis of carbethoxymethyltriethylammonium iodide by sodium hydroxide.

$10^3 a$.	Added salt.	Ionic strength (I).	k.	$10^3 a$.	Added salt.	Ionic strength (I).	k.
5·66	—	0·0057	241	5·66	0·218M-NaCl	0·224	142
5·91	—	0·0059	254	5·66	0·0726M-$CaCl_2$	0·224	104
3·30	0·0234M-NaCl	0·0267	202	4·22	0·274M-NaCl	0·278	136
5·60	0·118M-NaCl	0·124	169	4·22	0·0913M-$BaCl_2$	0·278	127
6·10	0·175M-NaCl	0·181	156	3·98	0·291M-NaCl	0·295	140
6·10	0·0582M-$CaCl_2$	0·181	119	3·98	0·145M-NaCl	—	—
5·13	0·178M-NaCl	0·184	158		+0·0484M-$CaCl_2$	0·295	115
5·13	0·0395M-$BaCl_2$	0·184	154	3·98	0·0969M-$CaCl_2$	0·295	93

The solubility of calcium iodate in colutions of sodium chloride and hydroxide at 0° was measured exactly as described by Davies (*J.*, 1938, 277), using a Dewar flask containing ice and water as a thermostat, and excluding carbon dioxide from the saturator. The values obtained are given in the first two columns of Table II. In interpreting the results it is necessary to make a small correction for the presence of the species $CaIO_3^+$ and $NaIO_3$, and for this purpose we have used the thermodynamic dissociation constants given by Davies (*loc. cit.*) for 25°, $K(CaIO_3^+) = 0{\cdot}13$, $K(NaIO_3) = 3{\cdot}0$. The thermodynamic solubility product of calcium iodate, $P[Ca(IO_3)_2]$, is obtained by extrapolating to $I = 0$ the measured solubilities in water and in dilute sodium chloride solutions. The ionic strengths are sufficiently low for the limiting law to be obeyed, and the resulting values are $s_0 = 1{\cdot}940 \times 10^{-3}$, $P = 4s_0^3 = 2{\cdot}921 \times 10^{-9}$. The concentrations of the various species present are then given by the equations

$$\left.\begin{aligned} \log_{10}[NaIO_3] &= \log_{10}[Na^+] + \log_{10}[IO_3^-] - \log_{10}K(NaIO_3) - f(I) \\ \log_{10}[CaIO_3^+] &= \log_{10}[Ca^{++}] + \log_{10}[IO_3^-] - \log_{10}K(CaIO_3^+) - 2f(I) \\ \log_{10}[Ca^{++}] &= \log_{10}P[Ca(IO_3)_2] - 2\log_{10}[IO_3^-] + 3f(I) \\ 2s &= [IO_3^-] + [NaIO_3] + [CaIO_3^+] \end{aligned}\right\} \quad . \quad . \quad . \quad . \quad (1)$$

together with the condition for electrical neutrality and a knowledge of the total amount of sodium added. s is the measured solubility in moles per litre, and $f(I)$ is a function representing the

dependence of the ionic activity coefficients on ionic strength. For $f(I)$ we have used two alternative expressions,

$$\left.\begin{array}{ll} (a)\ f(I) = -\log_{10} f = 0{\cdot}490\ I^{\frac{1}{2}}/(1 + I^{\frac{1}{2}}) \\ (b)\ f(I) = -\log_{10} f = 0{\cdot}490\ I^{\frac{1}{2}}/(1 + I^{\frac{1}{2}}) - 0{\cdot}2\ I \end{array}\right\} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

By use of either of these, the equations in (1) can be solved by successive approximations, and the concentrations of $CaOH^+$ and OH^- calculated by difference. An approximate value for the thermodynamic dissociation constant of $CaOH^+$ is then given by

$$\log_{10} K'_4 = \log_{10}[Ca^{++}] + \log_{10}[OH^-] - \log_{10}[CaOH^+] - 2f(I) \quad . \quad . \quad . \quad . \quad (3)$$

FIG. 1.

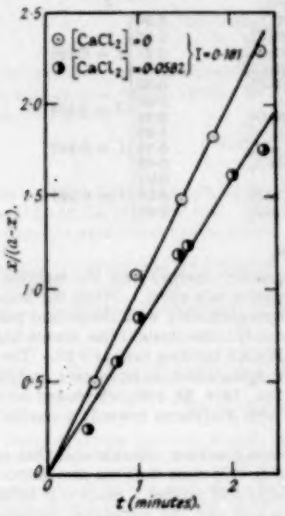
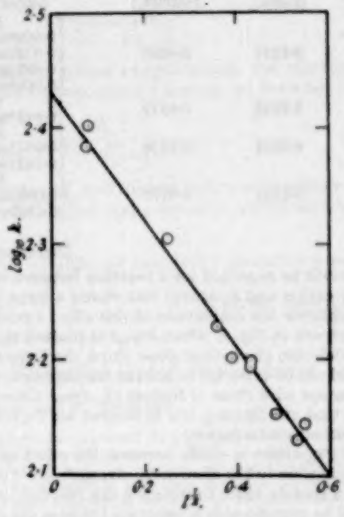


FIG. 2.



The values obtained are given in Table II. The mean values of K'_4 do not differ much from the value 0·03 at 25° obtained by the same method by Davies.

TABLE II.

Solubility of calcium iodate at 0°.

10^3[NaCl].*	$10^3 s$.	10^3[$NaIO_3$].	10^3[$CaIO^+_3$].	10^3[$CaOH^+$].	I.	K'_4.
—	2·333	—	—	—	0·0070	—
1·000	2·371	—	—	—	0·0081	—
2·000	2·423	—	—	—	0·0093	—
3·000	2·459	—	—	—	0·0104	—
4·000	2·488	—	—	—	0·0115	—
10^3[NaOH].*						
18·16	2·836	(*a*) 0·025	(*a*) 0·054	(*a*) 0·415	(*a*) 0·0257	(*a*) 0·054
		(*b*) 0·025	(*b*) 0·054	(*b*) 0·510	(*b*) 0·0255	(*b*) 0·043
31·37	3·093	(*a*) 0·044	(*a*) 0·054	(*a*) 0·601	(*a*) 0·0397	(*a*) 0·060
		(*b*) 0·045	(*b*) 0·053	(*b*) 0·737	(*b*) 0·0394	(*b*) 0·047
45·40	3·350	(*a*) 0·065	(*a*) 0·052	(*a*) 0·897	(*a*) 0·0535	(*a*) 0·052
		(*b*) 0·067	(*b*) 0·051	(*b*) 1·063	(*b*) 0·0532	(*b*) 0·042
68·10	3·606	(*a*) 0·098	(*a*) 0·052	(*a*) 1·014	(*a*) 0·0767	(*a*) 0·063
		(*b*) 0·102	(*b*) 0·050	(*b*) 1·266	(*b*) 0·0762	(*b*) 0·046
					Mean {	(*a*) 0·057
						(*b*) 0·044

* Denotes stoicheiometric concentration.

The alkaline hydrolysis of ethyl acetate was studied at 25° by the usual titration method, using approximately 0·02M-concentrations of ester and sodium hydroxide. Experiments with varying

quantities of added sodium chloride up to 0·8M. gave the following values (in order of increasing ionic strength) for the second-order velocity constant k (minutes, moles/l.): k = 5·92, 5·97, 5·90, 6·04, 6·05, 5·95, 5·99, 5·93, 6·01. There is thus no detectable salt effect under these conditions. Experiments were also done with varying additions of barium chloride and calcium chloride, and in each group of these experiments the ionic strength was made up to a constant value by the addition of sodium chloride. The results are given in Table III. It will be seen that the effect of barium chloride is to increase the velocity slightly, whereas calcium chloride had no detectable effect. In neither case is there any decrease which could be related to the incomplete dissociation of barium or calcium hydroxide.

TABLE III.

Hydrolysis of ethyl acetate at 25°.

[Ester.]	[NaOH.]	Added salt.	k.	
0·0111	0·0207	Nil	5·90	I = 0·198
		0·0099M-$BaCl_2$	5·92	
		0·0197M-$BaCl_2$	6·21	
		0·0394M-$BaCl_2$	6·31	
		0·0592M-$BaCl_2$	6·50	
0·0219	0·0219	Nil	5·92	I = 0·153
		0·0437M-$BaCl_2$	6·38	
0·0159	0·0159	Nil	5·99	I = 0·442
		0·0711M-$CaCl_2$	5·78	
		0·1421M-$CaCl_2$	5·63	
0·0117	0·0117	Nil	6·01	I = 0·489
		0·0995M-$CaCl_2$	6·03	
		0·1592M-$CaCl_2$	5·97	

DISCUSSION.

As would be expected for a reaction between oppositely charged ions, the reaction between the ester cation and hydroxyl ions shows a large negative salt effect. When the added salt is sodium chloride the magnitude of this effect agrees approximately with theoretical predictions. This is shown in Fig. 2, where $\log_{10}k$ is plotted against $I^{\frac{1}{2}}$: the straight line drawn has a slope of 0·6, while the theoretical slope (from the Debye–Hückel limiting law) is 0·98. The limiting law would not be expected to hold at the high ionic strengths which we have used, and our results are consistent with those of Nielsen (*J. Amer. Chem. Soc.*, 1936, **58**, 206), who found for the same reaction that the limiting law is obeyed for I<0·1, with deviations towards a smaller slope in more concentrated solutions.

If a comparison is made between the effect of adding sodium chloride and that of adding calcium chloride to the same ionic strength (cf. Table I), it is clear that the presence of calcium ions has a specific effect in reducing the reaction velocity still further. Since it is unlikely that there will be considerable interaction between calcium ions and the uncharged transition state, the simplest explanation of the reduced velocity is the removal of some hydroxyl ions as the species $CaOH^+$. In our experiments the concentration of Ca^{++} was considerably greater than that of OH^-, and under these conditions it is easily seen that the replacement of Na^+ by Ca^{++} at constant ionic strength will reduce the velocity by a factor $1 + [Ca^{++}]/K_c$, where $K_c = [Ca^{++}][OH^-]/[CaOH^+]$. The values of K_c can thus be obtained directly from the observed reaction velocities, and are given in the fifth column of Table IV. They can be converted into approximate thermodynamic dissociation constants K'_d by the use of equation (3), and the resulting values [obtained with the alternative expressions 2(*a*) and 2 *b*) for $f(I)$] are given in the last column of Table IV.

TABLE IV.

Hydrolysis of carbethoxymethyltriethylammonium iodide by sodium hydroxide.

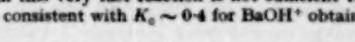
				K'_d.	
I.	[$CaCl_2$.]	k.	K_c.	(*a*).	(*b*).
0·181	0	156	—	—	—
	0·0582	119	0·19	0·049	0·058
0·224	0	142	—	—	—
	0·0726	104	0·20	0·047	0·058
0·295	0	140	—	—	—
	0·0484	115	0·23	0·047	0·061
	0·0969	93	0·20	0·041	0·057
			Mean	0·046	0·056

The values obtained for K'_d are close to those derived from the solubility measurements at the same temperature (cf. Table II), though the order of the constants from assumptions (*a*) and

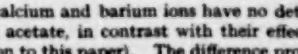
(*b*) is reversed. The discrepancy is not greater than would be expected in extrapolating from the high ionic strengths used in the kinetic measurements.

The results with added barium salts (cf. Table I) show a small retarding effect, but the accuracy of measurements in this very fast reaction is not sufficient to justify a quantitative treatment. The results are consistent with $K_a \sim 0{\cdot}4$ for $BaOH^+$ obtained previously (Bell and Prue, and Davies, *locc. cit.*).

It remains to consider why calcium and barium ions have no detectable retarding effect in the alkaline hydrolysis of ethyl acetate, in contrast with their effect in the decomposition of diacetone alcohol (cf. introduction to this paper). The difference probably lies in the transition states of the two reactions. In the diacetone alcohol decomposition the transition state can be written



where the negative charge is shared between two distant oxygen atoms, and the tendency to associate with cations will be small. In the hydrolysis of ethyl acetate, on the other hand, the transition state will be



where the negative charge is much more concentrated, and the association with cations may well resemble that of the hydroxyl ion. It is probable that some reactions will exhibit behaviour intermediate between these two extremes.

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PHYSICAL CHEMISTRY LABORATORY, OXFORD. [*Received, April 5th*, 1950.]

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405. *The Constitution of the Disaccharide of Glycyrrhinic Acid.*

By B. LYTHGOE and S. TRIPPETT.

Glycyrrhinic acid has been studied by periodate oxidation and by degradation of *trimethyl glycyrrhinate pentamethyl ether* and shown to have the structure (XIII) in which two glucopyruronic acid residues are joined by a β-1′ : 2-link. A method for the identification of methylated uronic acid derivatives has been elaborated in which they are converted into methylated aldoses by making use of lithium aluminium hydride to effect the reduction $CO_2Me \longrightarrow CH_2{\cdot}OH$.

GLYCYRRHINIC ACID, the acidic saponin of liquorice root, contains the triterpene acid glycyrrhetic acid attached glycosidically to a disaccharide composed of two hexuronic acid units. The disaccharide was isolated in the form of its methylglycoside dimethyl ester by Voss and Pfirschke (*Ber.*, 1937, **70**, 132). They did not investigate its structure and were not able to decide with certainty the nature of the uronic acid present; indeed, the rapid and extensive decarboxylation which they found to occur when the saponin was hydrolysed with dilute acids made it seem doubtful if any of the known uronic acids could be present. Earlier work had led Tschirsch and Gauchmann (*Arch. Pharm.*, 1908, **246**, 554) to think that the uronic acid was D-glucuronic acid, and Bergmann (*Biochem. Z.*, 1933, **267**, 304) to suggest that it was D-mannuronic acid.

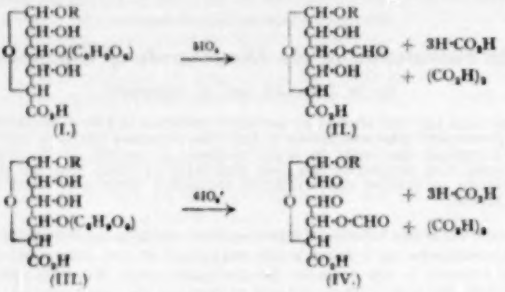
At first we were interested in glycyrrhinic acid as a possible model for centelloside, a saponin-like substance which we isolated from *Centella asiatica*; centelloside contains a hydroxylated triterpene carboxylic acid aglycone attached to a polysaccharide system. It soon became clear, however (Lythgoe and Trippett, *Nature*, 1949, **163**, 258), that the link between the aglycone and the carbohydrate in centelloside involves the carboxyl group of the former, not, as is usual in triterpene saponins, the alcoholic hydroxyl at $C_{(3)}$, so that an ordinary saponin could not be expected to provide an exact model for centelloside. Since little seems to be known about the oligosaccharides of saponins in general, and glycyrrhinic acid is relatively accessible and presents some interesting features, we decided to determine the nature of its sugar component. Our results are described in the present paper.

The oxidation of glycyrrhinic acid by sodium metaperiodate provided useful structural information. The aglycone, glycyrrhetic acid, was unaffected, but the intact glycoside con-

sumed 8 moles of the reagent. No formaldehyde was produced in the reaction, but 6 equivalents of strong acid were liberated, one of which was due to 1 mole of oxalic acid. These results cannot be reconciled with structures containing 2- or 5-ketohexuronic acid units, and support the views of earlier workers that the saponin contains an aldohexuronic acid.

Huebner and his collaborators (*J. Biol. Chem.*, 1945, **159**, 502; *J. Amer. Chem. Soc.*, 1947, **68**, 1621) found that bornyl-D-glucuronoside consumed 5 moles of periodate and liberated 4 equivalents of strong acid, one of which was due to 1 mole of oxalic acid; at the end of the reaction the aglycone was present as bornyl formate. The interpretation of these results which the authors provided shows the important part which the hydroxylation of suitably activated methylene groups may play in oxidations of this kind. There is an obvious resemblance between their results with bornylglucuronoside and our own with glycyrrhinic acid; both consume large amounts of the oxidant, and from both oxalic acid is liberated. At least one of the hexuronic acid units of glycyrrhinic acid must be pyranose to account for the formation of oxalic acid; in fact, both must be so, for no structure containing a furanose unit can be written which would consume more than 6 moles of oxidant. The formation of only 1 mole of oxalic acid indicated that only one of the hexuronic acid residues was degraded completely; this might leave its glycosidic carbon atom as a formyl group attached to the other unit, which would be thereby protected from complete oxidation. This point will be clear if reference is made to the structures (I) and (III), the behaviour of which on oxidation seems easily predictable.

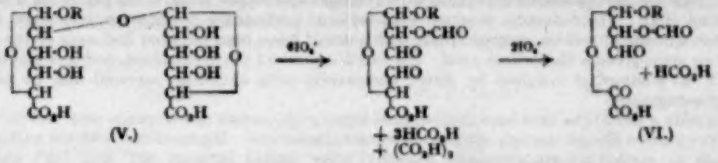
In the dihexuronoside (I) the two uronic acid residues are joined by a 1′ : 3-link. The residue written as $C_6H_9O_6$ should be completely oxidised in the way described by Huebner and his collaborators, giving (II), the formyl group of which should protect it against further attack. The dihexuronoside (III), in which the uronic acid residues are joined by a 1′ : 4-link, should suffer complete oxidation of the residue remote from the aglycone, and the residue proximate to the aglycone should consume an additional mole of oxidant to give (IV).



It was desirable that these ideas should be confirmed by experiment, since they would, if correct, exclude the structures (I) and (III) for glycyrrhinic acid. In order to test whether our experimental conditions caused degradation of a glucuronoside in a way similar to that observed by Huebner and collaborators, *triacetyl* cyclo*hexyl*-β-D-*glucuronoside* was synthesised by methods similar to those used for other uronic acid derivatives by Stacey and his co-workers (*J.*, 1939, 1529; *J.*, 1944, 131; compare Luckett and Smith, *J.*, 1940, 1114). The compound obtained by the removal of the acetyl groups from the synthetic triacetate consumed 5 moles of periodate. A representative dihexuronoside was synthesised from *hepta-acetyl* cyclo*hexyl*-β-D-*maltoside* by converting it into 2 : 3 : 2′ : 3′ : 4′-*penta-acetyl* cyclo*hexyl*-β-D-*maltoside*, which was oxidised by potassium permanganate to *penta-acetyl* 4-(α-D-*glucuronosyl*) cyclo*hexyl*-β-D-*glucuronoside*. The compound (III; R = C_6H_{11}) obtained on removal of the acetyl groups consumed, as expected, 6 moles of periodate.

There remained the possibility that the uronic acid residues of glycyrrhinic acid might be united by a 1′ : 2-link, as in (V), the oxidation of which might be expected to proceed as shown. When 8 moles of periodate have been reduced, the compound (VI) should result; it seemed probable that this would resist further attack, although, since it is an oxalic acid half ester, the possibility that it could undergo hydrolysis in the acidic reaction medium and so be oxidised more extensively, cannot altogether be discounted. However, since during the formation of

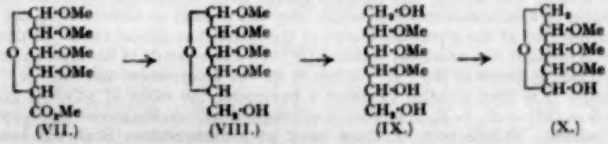
(VI) 5 equivalents of strong acid and a further 1 mole of oxalic acid would be formed, as actually found for glycyrrhinic acid, the structure (V) was adopted provisionally and gave valuable guidance in later experiments which proved it correct.



Thinking that some of the difficulties which Voss and Pfirschke encountered in characterising the uronic acid of glycyrrhinic acid might so be avoided, we preferred to work with methylated compounds. Methylation of the saponin as described in the Experimental section gave a crystalline *trimethyl glycyrrhinate pentamethyl ether*. This, like the saponin itself, could not be methanolised completely with 8% methanolic hydrogen chloride; after prolonged boiling the principal products were methyl glycyrrhetate and a *methyldihexuronoside dimethyl ester pentamethyl ether* possessing a resistant inter-uronic link. Spoehr (*Arch. Biochem.*, 1947, **14**, 153) found that alginic acid, which mineral acids hydrolyse only slowly and with extensive decarboxylation, can be hydrolysed with relatively little decomposition if 90% formic acid is used as the reagent. Both trimethyl glycyrrhinate pentamethyl ether and the methyldihexuronoside dimethyl ester pentamethyl ether were hydrolysed successfully by this reagent and, after the hydrolysis product from either compound had been treated first with methanolic hydrogen chloride and then with methanolic ammonia, two methylated carbohydrate fragments were isolated as crystalline amides. That more soluble in benzene (amide *A*) was the amide of a methylhexuronoside trimethyl ether and had m. p. 157—163°, $[\alpha]_D$ +106° (water). The less soluble component (amide *B*) was the amide of a methylhexuronoside dimethyl ether and had m. p. 193°. The latter was deaminated by nitrous fumes, and the resulting acid methylated with methyl iodide and silver oxide. Treatment of the product with methanolic ammonia gave a product identical with amide *A*, hence the two uronic acid units of glycyrrhinic acid must be identical.

Up to the present the amides of only three methylhexopyruronoside trimethyl ethers have been described. That derived from D-glucuronic acid has m. p. 183°, $[\alpha]_D$ +138° (water) (Smith, *J.*, 1939, 1724); that derived from D-mannuronic acid has not been obtained crystalline (compare Ault, Haworth, and Hirst, *J.*, 1935, 517); that derived from D-galacturonic acid has m. p. 154°, $[\alpha]_D$ +139° (water) (Luckett and Smith, *loc. cit.*). It appeared that amide *A* from glycyrrhinic acid could be identical with none of these, if the constants found for it were reliable. The rather wide temperature range over which it melted gave us some anxiety on this score, and we attempted to purify it by repeated recrystallisation and sublimation, but its constants remained unaltered, so we considered it to be pure. Experiments described below, by which its identity was established, show that we were mistaken in this.

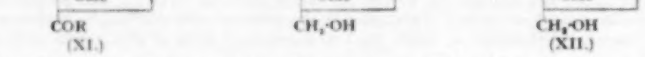
In the past, methylhexuronoside trimethyl ethers have been identified by converting them into the corresponding trimethoxyglutardiamides. The sequence of reactions shown below affords an alternative method of identification which is quite general and has marked advantages when rather small amounts of material are available for investigation. The reactions used give very high yields; the end-product from any methyl hexopyruronoside trimethyl ether is a trimethyl pentopyranose; at least one of the two enantiamorphous trimethyl ethers corresponding to each of the four aldopentoses is known and crystalline, and these compounds are moreover, readily identified by paper chromatography.



In order to apply this method, amide *A* was deaminated with nitrous fumes and the free acid converted by diazomethane into its methyl ester, which was purified by distillation.

Treatment of the methyl ester (VII) with lithium aluminium hydride gave the primary alcohol (VIII) as a gum which failed to give the naphtharesorcinol test, showing that the reduction was complete. Hydrolysis with dilute acid removed the glycosidic methyl group from (VIII), and the crude reaction product was reduced with hydrogen and Raney nickel to the partly methylated hexitol (IX). The reduction product, used without preliminary purification, consumed 60% of the amount of sodium metaperiodate which would have been required had each of the preceding steps given a theoretical yield; the reaction product (X) crystallised, and was identified as 2 : 3 : 4-trimethyl L-xylose by direct comparison with authentic material and by paper chromatography.

Amide *A* must thus have been derived from either D-glucuronic or L-iduronic acid, and its high dextrorotation argued strongly against the second alternative. Mixtures of it with the authentic amide of methyl-α-D-glucuronoside trimethyl ether melted between 163° and 183°, and in spite of the wide divergence in the constants of the two samples there can be no doubt that they were essentially the same substance; clearly the sample from the saponin was contaminated by a small quantity of the β-isomer. We had been led by the literature (*e.g.*, Smith, *loc. cit.*) to believe that when 2 : 3 : 4-trimethyl D-glucuronic acid is boiled with methanolic hydrogen chloride the α-form of the methylglycoside methyl ester predominates very greatly in the product. Our experience shows that this predominance is by no means always so great as we had expected, and it is noteworthy that Hirst and Jones (*J.*, 1938, 1174) isolated from a methylated aldobiuronic acid a sample of the amide of methyl-D-glucuronoside trimethyl ether having m. p. 158°, $[\alpha]_D$ +60° (water), which was a mixture of α- and β-forms which could not be separated by crystallisation. Since amide *B* from glycyrrhinic acid gave, when converted into amide *A*, material with a low optical rotation, it seems likely that, in spite of its sharp melting point, it too may be an α-form contaminated with traces of the β-isomer.



(XI.) (XII.)

If the interpretation of the periodate oxidation experiments given above is correct, amide *B* must be the amide of 3 : 4-dimethyl methyl-D-glucuronoside (XI; R = NH_2). It was converted into the methyl ester (XI; R = OMe) which was reduced with lithium aluminium hydride to the corresponding alcohol, acidic hydrolysis of which gave crystalline 3 : 4-dimethyl D-glucose. This was identified by comparison with a specimen kindly supplied by Drs. Bell and Greville of the Biochemistry Department. They have shown (forthcoming publication) that their material is identical with the original product of Dewar and Fort (*J.*, 1944, 496), but that the latter authors gave incorrect values for its optical rotation. Our product had the same optical constants as those found by Bell and Greville.

Glycyrrhinic acid thus contains two 1′ : 2-linked glucuronic acid units. With regard to the stereochemistry of the glycosidic links Voss and Pfirschke suggested that the difficultly methanolysed interuronic link was of the β-, the other of the α-type; we find that the former assignment is supported by optical-rotation data.

Isorotation rules have often been applied to disaccharides; the method used here, which applies to disaccharides of the trehalose type and to methyl-glycosides of reducing disaccharides, but more particularly to the fully methylated derivatives of both classes, is merely an extension of that of Charlton, Haworth, and Hickinbottom (*J.*, 1927, 1527; compare Haworth and Hirst, *J.*, 1930, 2615). We make the assumption, which is supported by considerable evidence, that methyl and glycosyl groups make approximately equal contributions to the rotation of a monosaccharide in which they are present as substituents, not only when they are substituted at the glycosidic centre of the latter, but also at other positions. If this assumption is justified, the molecular rotation $[M]$ of a disaccharide of the type under discussion can be expressed in terms of the "*B*" values of its two components and the "*A*" value of a methyl group; it is then possible to define a parameter the value of which is given by the expression $S = [M] - B_1 - B_2$, such that S will depend only on the stereochemistry of the two glycosidic centres. Where both of these have an α-configuration S should have a value approximately the same as $2A_{Me}$; where both have a β-configuration $S \approx -2A_{Me}$; where one has an α-, the other a β-configuration $S \approx$ zero.

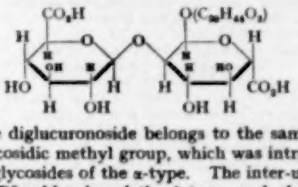
The extent to which the original assumption is justified can be judged from the table, in which some *S* values, relating to aqueous solutions and the sodium D line, are assembled. All those methylated derivatives for which the necessary data are available have been included. The following values, calculated from rotations recorded in Beilstein's Handbuch, IVth Edition, vol. XXXI, have been used in the calculations: "*A*" values: Me, +18,700°. "*B*" values: glucose, +12,100°; galactose, +19,000°; methylated glucose, +16,300°; methylated galactose, +21,000°.

Compound.	$[\alpha]_D$ (in water).	$[M]$.	*S*.
αα-Trehalose	+197°	+67,400°	+43,200°
Methyl-α-D-gentiobioside	+65·5	+23,300	− 900
Methyl-β-D-maltoside	+78·8	+28,100	+ 3,900
Heptamethyl methyl-β-D-maltoside	+88·1	+40,000	+ 7,400
Heptamethyl methyl-β-D-melibioside	+97·8	+44,000	+ 7,100
Heptamethyl methyl-β-D-lactoside	−16·9	− 7,700	−45,000
Heptamethyl methyl-β-D-cellobioside	−19·1	− 8,700	−41,300
Heptamethyl methyl-β-D-gentiobioside	−36	−16,400	−49,000

No fully methylated representative with two α-links is available, so the *S* value (+43,200°) for αα-trehalose has been included, and may be compared with the theoretical value, +37,400°. Values of *S* for compounds containing one α- and one β-link range from −900° to +7,400° (theoretical, zero); those for compounds with two β-links range from −41,300° to −49,000° (theoretical, −37,400°). Individual variations from the theoretical values in each class are, as might be expected, considerable; but this does not invalidate the point we wish to establish, which is that *S* values do allow disaccharide derivatives to be assigned unambiguously to one of three classes, depending only on the types of the glycosidic links present.

In order to apply this method to the problem in hand, the "*B*" value for a fully methylated D-glucuronoside methyl ester is required. Smith (*loc. cit.*) records for methyl-α-D-glucuronoside methyl ester trimethyl ether, $[\alpha]_D$ +87°, corresponding to $[M]$ +23,000°; this value is undoubtedly somewhat low, since it relates to a syrupy product prepared by a method which must lead to the presence of small amounts of the β-isomer. By subtracting A_{Me} (+18,700°) we obtain for the desired *B* value +4,300°, which again is probably too low, but is unlikely to be sufficiently so to invalidate configurational deductions from it. It is of interest as a test to apply this *B* value to the 6-(β-D-glucuronosyl) methyl-β-D-galactoside methyl ester hexamethyl ether obtained from gum arabic by Challinor, Haworth, and Hirst (*J.*, 1931, 258). This compound has $[\alpha]_D$ −21° ($[M]$ −9,800°), giving $S = -9,800 - 4,300 - 21,000 = -35,100°$. Although this value is, as expected, somewhat low numerically, it is sufficient to show unambiguously the presence of two β-links in the aldobiuronoside.

Applying the method now to the methyldiglucurosonide methyl ester pentamethyl ether from glycyrrhinic acid, which has $[\alpha]_D$ +38·5° ($[M]$ +18,600°) we obtain $S = +18,600 - 2(4,300) = +10,000°$; this value will be rather higher than the true one for reasons already given, but it is sufficiently close to the values obtained for compounds containing one α- and



(XIII.)

one β-link to show that the diglucuronoside belongs to the same class. The α-link is clearly that which attaches the glycosidic methyl group, which was introduced by a method known to give rise predominantly to glycosides of the α-type. The inter-uronic acid link must therefore, as suggested by Voss and Pfirschke, be of the β-type, and glycyrrhinic acid must have the structure (XIII).

Experimental.

Isolation of Glycyrrhinic Acid.—The method of Tschirsch and Cederburg (*Arch. Pharm.*, 1907, **245**, 97) was used, with modifications only in detail, for the isolation of glycyrrhinic acid from commercial "glycyrrhizinum ammoniacale," and proved more satisfactory than that of Voss, Klein, and Sauer (*Ber.*, 1937, **70**, 122). From the commercial drug (1 kg.) crude ammonium glycyrrhinate was obtained which separated from glacial acetic acid as light brown crystals (80 g.), $[\alpha]_D^{17}$ +40° (*c*, 3·0 in 40% alcohol). This material was converted into the lead salt and thence into the free acid, which was obtained pure and colourless by recrystallisation from glacial acetic acid and had $[\alpha]_D^{17}$ +46·2° (*c*, 1·5 in alcohol). The pure acid, treated with alcoholic ammonia, gave ammonium glycyrrhinate as colourless needles (from

alcohol), $[\alpha]_D^{17}$ +43·2° (*c*, 2·9 in 40% alcohol). Voss, Klein, and Sauer record for this ammonium salt, $[\alpha]_D^{17}$ +43·3° (in 40% alcohol).

Periodate Oxidation of Glycyrrhinic Acid.—To a solution of glycyrrhinic acid (74·6 mg.) in a little water containing sodium hydroxide (1 equiv.) 0·23M-sodium metaperiodate (10 c.c.) was added, and the solution was diluted to 50 c.c. and kept at room temperature, aliquots being withdrawn for titration at intervals. The oxidation was complete after 24 hours, 8·27 mols. of oxidant per mol. of saponin having been consumed, and 6·2 equivs. of strong acid (methyl-red indicator) liberated. No formaldehyde could be found in the solution by the method of Reeves (*J. Amer. Chem. Soc.*, 1941, **63**, 1476).

In another experiment, ammonium glycyrrhinate (177·5 mg.) dissolved in water (5 c.c.) was treated with 0·23M-sodium metaperiodate (25 c.c.) and the solution kept at room temperature for 24 hours to complete the oxidation. The filtered solution was then treated with N-hydrochloric acid (6 c.c.) and iodate and periodate ions removed by titration with 1·2N-sodium arsenite. The solution was buffered to pH 7 by adding sodium acetate, treated with 5% aqueous calcium chloride (1 c.c.), and kept overnight. The precipitated calcium oxalate, collected, washed, and dissolved in warm dilute sulphuric acid, required 18·56 c.c. of 0·02N-potassium permanganate for its oxidation; this corresponds with 0·88 mols. of oxalic acid per mol. of saponin. Under similar conditions methyl-β-D-galacturonoside gave 0·80 mol. of oxalic acid per mol. of glycoside.

2 : 3 : 4-*Triacetyl* 6-*Trityl* cyclo*Hexyl-β-D-glucoside*.—*cyclo*Hexyl-β-D-glucoside (4·7 g.; Pacsu, *J. Amer. Chem. Soc.*, 1930, **52**, 2568) and triphenylmethyl chloride (5 g.) dissolved in dry pyridine (30 c.c.) were heated on a boiling water-bath for 2 hours, the solution was cooled to 0°, and acetic anhydride (12 c.c.) added. After being kept at room temperature overnight the solution was poured slowly into stirred ice-water (2 l.). The suspension was stirred for a further hour, and the solid collected and crystallised from ethanol. The 2 : 3 : 4-*triacetyl* 6-*trityl* cyclo*hexyl-β-D-glucoside* (9 g., 72%) had m. p. 146—147°, $[\alpha]_D^{17}$ −26·8° (*c*, 4·5 in chloroform) (Found: C, 70·8; H, 6·9. $C_{31}H_{34}O_9$ requires C, 70·7; H, 6·8%).

2 : 3 : 4-*Triacetyl* cyclo*Hexyl-β-D-glucoside*.—To a solution of the above trityl derivative (8·8 g.) in glacial acetic acid (35 c.c.) at 10° a solution of hydrogen bromide in acetic acid (3·1 c.c.; saturated at 0°) was added, and the solution was shaken for 1 minute, and filtered directly into ice-water (250 c.c.). The resulting suspension was extracted with chloroform, and the extract washed with sodium hydrogen carbonate solution and then with water and evaporated under reduced pressure. Crystallisation of the residue from ether gave the triacetate (5 g., 90%), m. p. 112—113°.

2 : 3 : 4-*Triacetyl* cyclo*Hexyl-β-D-glucuronoside*.—A solution of the above triacetate (2·3 g.) in glacial acetic acid (20 c.c.) was added to a stirred solution of potassium permanganate (0·5 g.) in dry acetone (20 c.c.) and stirring continued for 40 hours whilst more permanganate (1·5 g. in 60 c.c. of acetone) was added gradually. The suspension obtained after the addition of water (40 c.c.) was centrifuged and the supernatant solution evaporated under reduced pressure. The residual syrup was dissolved in chloroform, and the solution washed with dilute sulphuric acid and with water, dried, and evaporated. The syrup obtained in this way crystallised, and recrystallisation from ether–light petroleum (b. p. 60—80°) gave the *glucuronoside* (0·7 g., 30%) as fine needles, m. p. 176—177° (Found: C, 54·4; H, 7·0. $C_{18}H_{24}O_{12}$ requires C, 53·8; H, 6·5%). Treatment with diazomethane gave the *methyl* ester, long needles (from alcohol), m. p. 135—137°, $[\alpha]_D^{17}$ −36° (*c*, 2 in chloroform) (Found: C, 55·0; H, 6·9. $C_{19}H_{26}O_{12}$ requires C, 54·8; H, 6·7%). For periodate oxidation triacetyl *cyclo*hexyl-β-D-glucuronoside (45 mg.) was dissolved in dry methanol (10 c.c.) containing sodium methoxide (from 50 mg. of sodium). The solution was kept at 0° for 6 hours and then neutralised with N-hydrochloric acid, and the alcohol evaporated under reduced pressure. After the addition of 0·23M-sodium metaperiodate (5 c.c.) the solution was made up to 25 c.c. and kept at room temperature, the progress of the oxidation being followed by the titration of aliquots. Reaction ceased after 60 hours, when 5·1 mols. of oxidant per mol. of glucuronoside had been consumed.

Penta-acetyl 4-(α-D-*Glucuronosyl*) cyclo*Hexyl-β-D-glucuronoside*.—Interaction of acetobromomaltose and *cyclo*hexanol in the usual manner gave *hepta-acetyl* cyclo*hexyl-β-D-maltose*, m. p. 137—139°, $[\alpha]_D^{17}$ +41·5° (*c*, 2 in chloroform) (Found: C, 52·3; H, 6·6. $C_{32}H_{48}O_{18}.H_2O$ requires C, 52·4; H, 6·6%). *cyclo*Hexyl-β-D-maltoside was obtained only as a syrup by the action of methanolic sodium methoxide on the hepta-acetate; it was converted by methods exactly similar to those described above into 2 : 3 : 2' : 3' : 4'-*penta-acetyl* cyclo*hexyl-β-D-maltoside*, m. p. 159—160° (Found: C, 53·4; H, 6·9. $C_{32}H_{44}O_{17}$ requires C, 53·0; H, 6·7%). By oxidation with potassium permanganate the *penta-acetyl* cyclo*hexyldihexuronoside* was obtained. It separated from alcohol as crystals which sintered at 175°, m. p. 185—187°, $[\alpha]_D^{18}$ +47·2° (*c*, 2·2 in chloroform) (Found: C, 49·7; H, 6·5. $C_{32}H_{44}O_{18}.H_2O$ requires C, 49·4; H, 5·9%). Treatment with diazomethane gave the *dimethyl* ester, m. p. 169—171° (from alcohol) (Found: C, 52·5; H, 6·4. $C_{36}H_{52}O_{18}$ requires C, 52·2; H, 6·1%).

For the periodate oxidation the penta-acetyl *cyclo*hexyldihexuronoside (75 mg.) was deacetylated with methanolic sodium methoxide, the neutralised solution freed from methanol and after the addition of 0·23M-sodium metaperiodate (5 c.c.) diluted to 25 c.c. and kept at room temperature. The oxidation was complete after 36 hours, 6·0 mols. of oxidant per mol. of the diglucuronoside having been consumed.

Trimethyl Glycyrrhinate Pentamethyl Ether.—Ammonium glycyrrhinate (4 g.) dissolved in 40% alcohol (50 c.c.) was treated with 0·8N-thallous hydroxide (8 mols. per mol. of saponin) and the pale yellow precipitate collected, washed, and dried to constant weight at room temperature over phosphoric oxide. The finely powdered thallous derivative was heated under reflux with methyl iodide, with exclusion of light and moisture for 8 hours, and the suspension filtered. The filtrate was evaporated, the residue extracted with chloroform, and the chloroform solution evaporated to a syrup. Two further methylations of the syrupy product with methyl iodide and silver oxide gave a *product* which crystallised from alcohol in flat leaves. The pure material (2·8 g., 60%) had m. p. 275—276°, $[\alpha]_D^{18}$ +34·3° (*c*, 1·1 in

chloroform) (Found: C, 62·8; H, 8·0; OMe, 25·2. $C_{20}H_{32}O_{10}.H_2O$ requires C, 63·0; H, 8·4; OMe, 26·1%).

Methanolysis of Trimethyl Glycyrrhinate Pentamethyl Ether.—A suspension of the above compound (4·6 g.) in 8% methanolic hydrogen chloride (150 c.c.) was heated under reflux for 12 hours, and all dissolved. The hydrogen chloride was neutralised with freshly prepared silver carbonate, the suspension filtered, and the filtrate evaporated under reduced pressure to a partly crystalline residue. After as much as possible of the methyl glycyrrhetate had been removed by crystallisation from the minimum amount of alcohol the mother-liquors were evaporated under reduced pressure to a syrup, which by distillation at 10^{-3} mm. furnished two fractions. Fraction 1 (0·4 g.), b. p. 120—140° (bath-temp.), had OMe, 52·9%; Fraction 2 (0·9 g.), b. p. 170—190°, had OMe, 49·3%. When Fraction 2 was dissolved in warm light petroleum (b. p. 60—80°) the cooled solution deposited the *methyldihexuronoside dimethyl ester pentamethyl ether* as long rods, m. p. 94—95°, $[\alpha]_D^{17}$ +36° (*c*, 2 in chloroform); +38·5° (*c*, 1 in water) (Found: C, 50·3; H, 7·2; OMe, 50·0. $C_{20}H_{34}O_{12}$ requires C, 49·8; H, 7·1; OMe, 51·4%).

Hydrolysis of the Methyldihexuronoside Dimethyl Ester Pentamethyl Ether with 90% Formic Acid.—The above dimethyl ester (1 g.) and 90% formic acid (30 c.c.) were heated together under reflux for 16 hours and after evaporation of the solution under reduced pressure the last traces of formic acid were removed by repeated evaporation of the residue with alcohol. The syrupy product was heated under reflux for 12 hours with 2% methanolic hydrogen chloride, the acid was removed by treatment with silver carbonate, and solvents were removed from the filtered solution under reduced pressure. When the residual syrup was distilled at 10^{-4} mm. only one fraction (0·7 g.) was obtained, b. p. 130—140° (bath-temp.); this material was kept at 0° for 4 days with methanolic ammonia (10 c.c.; saturated at 0°). When the solvent was removed a solid remained which was extracted with hot benzene (100 c.c.). The residue was recrystallised from ethyl acetate, giving the *methylhexuronoside dimethyl ether amide* (0·13 g.), m. p. 191—193°, $[\alpha]_D^{17}$ +100° (*c*, 2·5 in water) (Found: C, 46·2; H, 7·1; N, 6·0; OMe, 38·3. $C_9H_{17}O_6N$ requires C, 46·0; H, 7·2; N, 6·0; OMe, 39·5%). Evaporation of the benzene extract and crystallisation of the residue from light petroleum (b. p. 100—120°) gave the amide of a methylhexuronoside trimethyl ether (0·4 g.) as long needles, m. p. 157—163°, $[\alpha]_D^{17}$ +106° (*c*, 1 in water), +85° (*c*, 0·3 in chloroform) (Found: C, 48·6; H, 7·3; N, 5·3. Calc. for $C_{12}H_{23}O_6N$: C, 48·2; H, 7·6; N, 5·6%). These constants were altered neither by sublimation in a vacuum nor by fractional crystallisation from light petroleum (b. p. 100—120°).

Conversion of the Amide of the Methylhexuronoside Dimethyl Ether into that of the Methylhexuronoside Trimethyl Ether.—A stream of dry nitrous fumes was passed through a solution of the amide of the methylhexuronoside dimethyl ether (0·1 g.) in glacial acetic acid (3 c.c.) till it assumed a permanent green colour. The solution was kept at 0° for 2 hours and then evaporated under reduced pressure, and the residue evaporated repeatedly with alcohol. Methylation of the syrupy product with methyl iodide and silver oxide in the usual way gave a syrup which was kept at 0° for 4 days with methanolic ammonia (3 c.c.; saturated at 0°). Solvents were removed and the residue was crystallised from light petroleum (b. p. 100—120°), the amide of the methylhexuronoside trimethyl ether being obtained as long needles, m. p. 163°, $[\alpha]_D^{17}$ +110° (*c*, 1·2 in water).

Identification of the Methylhexuronoside Trimethyl Ether by the Conversion of its Amide into a Trimethyl Pentopyranose.—The amide of the methylhexuronoside trimethyl ether was deaminated with nitrous fumes as described above and the syrupy acid dissolved in ether and treated with an excess of diazomethane dissolved in ether. When the esterification was complete the solvent was removed and the product distilled at 10^{-4} mm. The main fraction (0·5 g.), b. p. 120° (bath-temp.), was dissolved in dry ether and the solution, after the addition of lithium aluminium hydride (0·5 g.), heated under reflux for 2 hours. The strongly cooled solution was treated with an excess of dilute sulphuric acid, and the acid solution extracted continuously with ether for 24 hours. Evaporation of the extract gave a colourless syrup which was heated at 95° for 3 hours with N-hydrochloric acid. The acid was removed by treatment with silver carbonate, and silver ions by treatment with hydrogen sulphide; when the filtered solution was evaporated under reduced pressure a colourless syrup remained which had strong reducing properties. It was dissolved in water (50 c.c.) and hydrogenated at 120°/100 atm. for 12 hours in the presence of Raney nickel catalyst (1 g.). After the catalyst had been removed and the solvent evaporated a non-reducing syrup (0·5 g.) remained which was dissolved in water and treated with a 10% excess of 0·23M-sodium metaperiodate. After 12 hours N-hydrochloric acid (5 c.c.) was added and the iodate and excess of periodate were removed by titration with 1·2N-sodium arsenite. The product, isolated by continuous extraction with ether, was a syrup (0·3 g.) which had strong reducing properties. Paper chromatography of this material against the four trimethyl pentopyranoses in both *n*-butanol and *s*-collidine showed that it contained one reducing substance only, which in these solvents travelled at the same speed as trimethyl D-xylopyranose. The syrup crystallised from ethyl acetate, giving trimethyl L-xylopyranose, m. p. 85—86°, undepressed on admixture with authentic material, m. p. 91°, but depressed on admixture with the D-isomer.

Conversion of the Amide of the Methylhexuronoside Dimethyl Ether into a Dimethyl Hexose.—The amide of the methylhexuronoside dimethyl ether (0·3 g.) was deaminated with nitrous fumes as already described and the free acid heated under reflux with 2% methanolic hydrogen chloride (30 c.c.) for 12 hours so as to convert it into the methyl ester. This was isolated by removing the acid with silver carbonate and evaporating the filtered solution under reduced pressure to a syrup. A solution of the latter in dry ether (20 c.c.) was added slowly to a solution of lithium aluminium hydride (0·5 g.) in ether (20 c.c.) which was maintained under reflux. Heating was continued for 2 hours, the cooled solution was treated with an excess of dilute sulphuric acid, and the syrupy product (0·3 g.) isolated by continuous extraction with ether. It was heated at 100° for 3 hours with N-hydrochloric acid, the acid was removed with silver carbonate, and silver ions were removed with hydrogen sulphide. Evaporation of the finally filtered solution under reduced pressure gave a syrup which crystallised from *iso*propyl

acetate in long needles, m. p. 119—120°, $[\alpha]_D^{20}$ +114·3° (5 minutes) ⟶ +77·5° (final value, 9 hours) (*c*, 1 in water) (Found : C, 46·1 ; H, 7·9. Calc. for $C_{19}H_{34}O_{14}$: C, 46·1 ; H, 7·7%). An authentic sample of 3 : 4-dimethyl D-glucose kindly supplied by Drs. Bell and Greville had m. p. 113°, $[\alpha]_D^{20}$ +98° (8 minutes) ⟶ +77·8° (final value, 9 hours) (water). Paper chromatography of the two samples in *n*-butanol and *s*-collidine gave additional confirmation of their identity.

We are grateful to Professor A. R. Todd, F.R.S., for his interest in this work, and to Professor M. Stacey and Dr. J. Dewar for samples of methyl-α-D-glucuronoside trimethyl ether and 3 : 4-dimethyl D-glucose. One of us (S. T.) thanks the Department of Scientific and Industrial Research for a Maintenance Grant. Assistance from Mr. D. K. Patel in some of the preliminary work is gratefully acknowledged.

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406. *Deoxyribonucleosides and Related Compounds. Part II. A Proof of the Furanose Structure of the Natural 2-Deoxyribonucleosides.*

By D. M. BROWN and B. LYTHGOE.

Ion-exchange methods have been used with advantage in isolating the pyrimidine deoxyribonucleosides from hydrolysates of deoxyribonucleic acid. The behaviour towards periodate of the 2'-deoxyribosides of guanine, hypoxanthine, cytosine, and thymine affords proof of their furanose structures.

THE widely-held view that the naturally occurring deoxyribonucleosides have furanose structures is based partly on the analogy with the related ribonucleosides, for which such structures are well established, and partly on the results of chemical studies of the compounds themselves. Levene and Tipson (*J. Biol. Chem.*, 1935, **109**, 623) found that the behaviour of certain triphenylmethyl and toluene-*p*-sulphonyl derivatives of thymidine indicated a furanose structure, and in agreement with this the conductivity of a boric acid solution was not increased by the presence of the nucleoside, showing the absence of a *cis*-1 : 2-glycol system (*idem, Z. physiol. Chem.*, 1935, **234**, v). The 2'-deoxyribosides of guanine and hypoxanthine were investigated by Makino (*Biochem. Z.*, 1935, **282**, 263), using the boric acid method, and found to behave similarly.

Attempts to synthesise 2'-deoxyribosides of purines and pyrimidines at present in progress in this laboratory made a more rigid proof of the ring-structures of the naturally occurring representatives desirable, and we have sought to obtain this by use of the periodate oxidation method which was found valuable in earlier work on natural and synthetic ribonucleosides (Lythgoe and Todd, *J.*, 1944, 592; Davoll, Lythgoe, and Todd, *J.*, 1946, 833). The 2'-deoxyribosides of guanine, hypoxanthine, thymine, and cytosine required for this work were obtained by enzymic hydrolysis of herring-sperm deoxyribonucleic acid. In agreement with Zittle (*Fed. Proc.*, 1947, **6**, 500), the phosphatase preparation from calf's intestinal mucosa which is usually used for this purpose (Klein, *Z. physiol. Chem.*, 1938, **255**, 82; Brady, *Biochem. J.*, 1941, **35**, 855) was found incapable of dephosphorylating the nucleic acid completely, and a preliminary treatment with a deoxyribonuclease preparation (McCarty, *J. Gen. Physiol.*, 1946, **29**, 123) was found advantageous. For the separation from the hydrolysate of the purine deoxyribosides a method recently described by Schindler (*Helv. Chim. Acta*, 1949, **32**, 979) was used successfully, but the chromatographic method which he employed to separate the pyrimidine derivatives was found to give only a partial resolution. Improved yields were obtained when this method was supplemented by that used by Elmore for the separation of cytidine and uridine (*Nature*, 1948, **161**, 931; cf. Harris and Thomas, *ibid.*; *J.*, 1948, 1936). This method which consists in the use of a column of a cation-exchange resin ("Zeo-Karb 215") gave a complete resolution of the two pyrimidine deoxyribosides and also allowed the cytosine deoxyriboside to be obtained pure directly, without the need for a preliminary isolation of the picrate as in Schindler's method.

If the natural deoxyribonucleosides have a furanoside structure they should be resistant to oxidation with sodium metaperiodate solution. In accord with this thymidine and cytosine deoxyriboside both consumed only a very small amount of the reagent (<0·1 mol. per mol. of glycoside) in 20 hours, after which reaction ceased. A possible explanation of this small but real initial uptake of oxidant may be that there was present in the periodate solution small amounts of other oxidising species which are non-specific for 1 : 2-glycol systems (cf. Head, *Nature*, 1950, **165**, 236). The purine deoxyribosides behaved rather unexpectedly, for, whilst

both of them showed a very small initial uptake of the oxidant during the first 20 hours, the reaction continued further, instead of terminating as with the pyrimidine compounds. The secondary phase of the oxidation of guanine deoxyriboside was rather slow, less than 0·5 mol. of oxidant per mol. of glycoside having been reduced after 400 hours, but the further oxidation of hypoxanthine deoxyriboside proceeded more rapidly as time went on and after 142 hours 2·4 mols. of oxidant per mol. of glycoside had been reduced. The autocatalytic nature of this reaction is probably attributable to the very labile character of the glycosidic link in hypoxanthine deoxyriboside; presumably a slow hydrolysis of this link takes place in the acidic reaction medium; the oxidation of the sugar set free in this way would then give rise to formic acid, thus leading to an acceleration of the hydrolysis and oxidation. It is significant that this phenomenon was not observed at all with the pyrimidine deoxyribosides, where the glycosidic link is known to be much more stable to hydrolysis than in the purine compounds.

These results afford confirmation of the furanoside nature of the natural deoxyribosides.

Experimental.

Isolation of the Deoxyribonucleosides.—Commercial herring-sperm deoxyribose nucleic acid was purified by the method of Sevag, Lackmann, and Smolens (*J. Biol. Chem.*, 1938, **124**, 425), and then had only a faintly positive biuret reaction and contained P, 7%. Its sodium salt (20 g.), dissolved in water (200 c.c.), was treated with a preparation of deoxyribonuclease (30 mg.), kindly provided by Mrs. B. Holmes of the Radiotherapeutics Department, and kept for 18 hours. The hydrolysis was then completed by the action of the phosphatase of calf's intestinal mucosa as described by Klein (*loc. cit.*); after 44 hours 96% of the total phosphorus present had been liberated as inorganic phosphate. From the hydrolysate the purine nucleosides were isolated by Schindler's method (*loc. cit.*). Guanine deoxyriboside was obtained as needles (45 mg.) from water (Found, in material dried over phosphoric oxide at 55°/1 mm.: C, 42·1; H, 5·0. Calc. for $C_{10}H_{13}O_4N_5,H_2O$: C, 42·1; H, 5·3%). Hypoxanthine deoxyriboside was obtained as small needles (600 mg.) from water (Found: C, 47·6; H, 5·2; N, 22·7. Calc. for $C_{10}H_{12}O_4N_4$: C, 47·6; H, 4·8; N, 22·2%).

Chromatography of the pyrimidine nucleoside-containing fraction on aluminium oxide by Schindler's method gave thymidine as long needles (215 mg.), m. p. 186°, from methanol–ether (Found: C, 49·7; H, 5·7. Calc. for $C_{10}H_{14}O_5N_2$: C, 49·6; H, 5·8%), and cytosine deoxyriboside as prisms (85 mg.), m. p. 210°, from methanol–ether (Found: C, 47·6; H, 5·9. Calc. for $C_9H_{13}O_4N_3$: C, 47·6; H, 5·8%).

Separation of Thymidine and Cytosine Deoxyriboside by Cation-exchange Column.—The residues from the fractions containing thymidine and cytosine deoxyriboside were combined, dissolved in distilled water, and allowed to percolate through a column (10 × 1 cm.) of "Zeo-Karb 215" resin (The Permutit Co. Ltd.) which had been activated by treatment with 3N-hydrochloric acid. The thymidine passed directly through the column and was obtained pure by evaporation of the effluent. After crystallisation from methanol–ether it was obtained as needles (1·5 g.), m. p. 186°. Elution of the column with 2% aqueous pyridine, and concentration of the eluate under reduced pressure gave cytosine deoxyriboside, which after crystallisation from methanol–ether formed needles (0·6 g.), m. p. 210°. Treatment of the mother-liquors with picric acid gave the picrate (0·27 g. of recrystallised material), from which the free nucleoside was conveniently regenerated as follows. A solution of the picrate (100 mg.) in water (50 c.c.) was allowed to percolate through a column (10 × 1 cm.) of "De-Acidite B" resin which had been activated by treatment with 2N-sodium hydroxide solution. The column was washed with water, and the effluent evaporated, crystallisation of the residue from methanol–ether giving cytosine deoxyriboside (37 mg., 75%) as prisms, m. p. 210°.

Sodium Metaperiodate Titrations.—Analytically pure specimens of the nucleosides (*ca.* 0·20 millimol.) were treated with 0·248M-sodium metaperiodate (5 c.c.), and the solution was diluted to 25 c.c. with water and kept at room temperature, aliquots being withdrawn for titration at intervals. Thymidine and cytosine deoxyriboside consumed 0·08 mol. of oxidant per mol. of glycoside during 18 hours; this value was unchanged after 92 hours. For hypoxanthine deoxyriboside the following values were obtained: Mol. of oxidant consumed per mol. of glycoside: after 22 hours, 0·10; 44 hours, 0·33; 94 hours, 0·89; 142 hours, 2·4. The reaction between guanine deoxyriboside and sodium metaperiodate was carried out in a solution which was 0·012M. with respect to the oxidant; after 21 hours 0·08, after 70 hours 0·10, after 169 hours 0·22, and after 408 hours 0·48 mol. of oxidant had been reduced per mol. of glycoside.

University Chemical Laboratory, Cambridge. [*Received, April 21st*, 1950.]

407. *Experiments on the Synthesis of Purine Nucleosides. Part XXVII. 1 : 2 : 3 : 5-Tetra-acetyl D-Xylofuranose and the D-Xylofuranosides of Theophylline and Adenine.*

By P. Chang and B. Lythgoe.

1 : 2 : 3 : 5-Tetra-acetyl D-xylofuranose has been synthesised from 5-trityl D-xylose and used for the preparation of the β-D-xylofuranosides of theophylline and adenine.

Methods for the preparation of tetra-acetyl pentofuranoses have been investigated in this laboratory because of the potential value of these compounds in the synthesis of furanose derivatives in general and of nucleoside analogues in particular; the preparation and the uses of tetra-acetyl D-ribofuranose have been reported in earlier papers of this series and recently (Bristow and Lythgoe, *J.*, 1949, 2306) we described the preparation of tetra-acetyl D-arabofuranose and its conversion into α-D-arabofuranosides of theophylline and adenine. These glycosides, and the corresponding xylofuranose analogues, are of particular interest in that they have a *trans*-1 : 2-glycol system, and should be able to form epoxides which might be of value in in the related field of deoxyribonucleoside synthesis (cf. Davoll and Lythgoe, *J.*, 1949, 2526). With this in mind we undertook the preparation of the D-xylofuranosides of theophylline and adenine.

The methods used in this work follow those found effective for the corresponding arabinose analogues, with modifications in detail. A necessary intermediate, 2 : 3 : 4-triacetyl 5-trityl D-xylose diethyl mercaptal (I; R = Ac), was prepared by Wolfrom, Quinn, and Christman

(*J. Amer. Chem. Soc.*, 1935, **57**, 713); in the Experimental section a modification of their procedure is described which gives this compound in an overall yield of 55% from D-xylose. The syrupy compound (I; R = H) obtained by deacetylation was converted by treatment with mercuric chloride and mercuric oxide in aqueous acetone into crystalline 5-trityl D-xylofuranose (II; R = H).

The amorphous triacetate (II; R = Ac) gave, on treatment with acetyl bromide by Bredereck and Hoepfner's method (*Ber.*, 1948, **81**, 50), 1 : 2 : 3 : 5-tetra-acetyl D-xylofuranose (III) which failed to crystallise, probably owing to the presence of both α- and β-forms. It was converted by ethereal hydrogen chloride into 2 : 3 : 5-triacetyl D-xylosyl chloride which, without being isolated pure, was used directly for the synthesis by standard methods of 7-β-D-xylofuranosyltheophylline (IV; R = $C_7H_7O_2N_4$) and 9-β-D-xylofuranosyladenine (IV; R = $C_5H_4N_5$). The configuration and ring-structure of these compounds was established by periodate oxidation; thus the theophylline compound consumed one molar proportion of the oxidant, gave no formic acid, and was converted into a crystalline dialdehyde, identical with that isolated after similar oxidation of 7-β-D-glucopyranosyltheophylline (Lythgoe and Todd, *J.*, 1944, 584).

Experimental.

2 : 3 : 4-*Triacetyl 5-Trityl* D-*Xylose Diethyl Mercaptal.*—Crude syrupy D-xylose diethyl mercaptal, prepared from D-xylose (47·5 g.) by the method of Wolfrom, Newlin, and Stahly (*J. Amer. Chem. Soc.*, 1931, **53**, 4379), was dissolved in pyridine (150 c.c.), and the ice-cold solution treated with acetic anhydride (200 c.c.), kept at room temperature for 24 hours, and poured into ice-water (3 l.). The product was extracted with chloroform, and the extract, after being washed and dried in the usual way, was evaporated under reduced pressure to a thick syrup which was then distilled at 10^{-4} mm. The distillate collected between 150° and 165° (bath-temp.) crystallised completely to a solid (80 g., 76%), m. p. 40—42°. Wolfrom, Newlin, and Stahly give for tetra-acetyl D-xylose diethyl mercaptal, recrystallised from aqueous methanol, m. p. 46—48°. The tetra-acetate (19·6 g.) was kept for 12 hours at room temperature with 6% methanolic ammonia (140 c.c.), solvents were removed under reduced pressure, and the residual syrup was dried by 2 evaporations with dry benzene. It was then dissolved in dry pyridine (50 c.c.), triphenylmethyl chloride (12·5 g.) added, and the solution kept at 20° for 24 hours and finally at 40° for 8 hours. Acetic anhydride (40 c.c.) was added to the cooled solution, which was then kept at 40° for 24 hours, cooled, and poured into ice-water. The product, isolated by extraction with chloroform in the usual way, was a syrup which crystallised from methanol in plates (22·7 g., 79%), m. p. 149—150°. Wolfrom, Quinn, and Christman (*loc. cit.*) record for this compound m. p. 150°.

5-Trityl D-*Xylofuranose*.—A solution of the above triacetate (42·5 g.) in chloroform (400 c.c.) was cooled to 0° and stirred mechanically whilst 0·4N-methanolic sodium methoxide (250 c.c.) was added slowly. The solution was kept at 0° for 12 hours, then shaken with several portions of ice-water until the chloroform phase was clear, the aqueous phases were extracted with a little chloroform, and the combined chloroform extracts dried and evaporated. The syrupy 5-trityl D-xylose diethyl mercaptal could not be obtained crystalline, so it was dissolved in acetone (330 c.c.) and water (33 c.c.), and the solution stirred vigorously with mercuric oxide (65 g.) whilst a solution of mercuric chloride (73·5 g.) in acetone (115 c.c.) was added during 2 hours. Stirring was continued for 24 hours, the solution filtered, and acetone removed from the filtrate under reduced pressure. The residue was diluted with water (500 c.c.) and extracted with chloroform (2 × 500 c.c.), the extract was washed once with 40% aqueous potassium iodide (200 c.c.) and twice with water (500 c.c.), dried (Na_2SO_4), and evaporated. The residual syrup crystallised slowly from ethyl acetate–light petroleum (b. p. 60—80°) giving *5-trityl* D-*xylofuranose* (19·5 g., 73%) as clusters of needles, m. p. 124—126°, $[\alpha]_D^{20}$ −14° (7 minutes) ⟶ −19·5° (final value, 90 minutes) (*c*, 3·17 in pyridine) (Found: C, 73·0; H, 6·8. $C_{24}H_{24}O_5$ requires C, 73·4; H, 6·2%). The crystalline material is clearly an α-form.

1 : 2 : 3 : 5-*Tetra-acetyl* D-*Xylose*.—The trityl compound (14 g.), pyridine (35 c.c.), and acetic anhydride (25 c.c.) were kept together at room temperature for 12 hours and the solution was poured slowly into cold water with efficient stirring. The white amorphous solid was collected and dissolved in hot alcohol, and the solution poured slowly into water with stirring. 2 : 3 : 5-*Triacetyl 5-trityl* D-*xylofuranose* (17·5 g.), which could not be crystallised, had $[\alpha]_D^{20}$ +33° (*c*, 1·9 in alcohol) (Found: C, 69·1; H, 5·7. $C_{30}H_{30}O_8$ requires C, 69·5; H, 5·8%). It was dissolved in acetic anhydride (32 c.c.) and to the solution acetyl bromide (5·2 c.c.) was added. After 30 minutes the solution was filtered from triphenylmethyl bromide, and the filtrate poured into ice-water (1 l.), whereupon triphenylcarbinol separated and was filtered off. The filtrate was extracted with chloroform, and the extract washed first with sodium hydrogen carbonate solution and then with water, dried, and evaporated under reduced pressure. The residue was distilled at 125—140° (bath-temp.)/6 × 10^{-4} mm., 1 : 2 : 3 : 5-*tetra-acetyl* D-*xylose* being obtained as a colourless syrup (7·4 g., 69%), $[\alpha]_D^{20}$ +56° (*c*, 2·17 in alcohol) (Found: C, 49·1; H, 5·5. $C_{13}H_{18}O_9$ requires C, 49·0; H, 5·7%).

7-β-D-*Xylofuranosyltheophyllins*.—A solution of the above tetra-acetate (1·18 g.) in ether (20 c.c.) was saturated with dry hydrogen chloride at 10° and kept at 0° for 4 days. The ether was then removed under reduced pressure and the residue evaporated thrice under reduced pressure with dry benzene in order to free it from hydrogen chloride. To the product a suspension of dry theophylline silver (2 g.) in dry xylene (40 c.c.) was added and the mixture was boiled under reflux for 2 hours and then filtered, and the filtrate evaporated to dryness under reduced pressure. The syrup so obtained did not crystallise and was therefore deacetylated by treatment with 6% methanolic ammonia (50 c.c.) at 0° for 24 hours. Evaporation of the solvent and crystallisation of the residue from water (2 c.c.) gave 7-β-D-*xylofuranosyltheophylline* as needles (570 mg., 50%), m. p. 230—232°, $[\alpha]_D^{20}$ +38° (*c*, 0·87 in water) (Found: C, 46·3; H, 5·1; N, 18·0. $C_{12}H_{16}O_6N_4$ requires C, 46·1; H, 5·2; N, 17·9%).

Oxidation of a portion of this material (75 mg.) with sodium metaperiodate (*ca.* 0·24M.) required 3 days for completion, and 1·02 mols. of oxidant per mol. of glycoside were reduced. The reaction solution deposited crystals which were dried in a vacuum-desiccator at room temperature and then had $[\alpha]_D^{17}$ −37° (*c*, 0·45 in water) and m. p. 206° (decomp.), undepressed on admixture with a specimen of the dialdehyde obtained from theophylline glucoside by Lythgoe and Todd (*loc. cit.*).

9-β-D-*Xylofuranosyladenine*.—Crude triacetyl D-xylofuranosyl chloride, prepared from tetra-acetyl D-xylofuranose (2·5 g.) as described above, was boiled under reflux for 5 hours with a suspension of dry 2 : 8-dichloroadenine silver (2·5 g.) in xylene (50 c.c.). To the cooled and filtered solution light petroleum (250 c.c.; b. p. 60—80°) was added and the powdery precipitate collected, washed with more light petroleum, and dried in the air. It was then kept with 10% methanolic ammonia (100 c.c.) at 0° for 18 hours, solvents were removed under reduced pressure, and the residue was crystallised from water, whereby 2 : 8-*dichloro*-9-β-D-*xylofuranosyladenine* was obtained as needles (1 g., 40%) which darkened and frothed at *ca.* 140° but had no definite m. p.; it had $[\alpha]_D^{20}$ −13·8° (*c*, 0·22 in water) (Found: C, 35·3; H, 3·4; N, 20·3. $C_{10}H_{11}O_4N_5Cl_2$ requires C, 35·7; H, 3·3; N, 20·8%).

When a portion (82 mg.) was treated with sodium metaperiodate solution, 0·99 mol. of the oxidant per mol. of glycoside was reduced after 7 days, and the fission product in the solution had $[M]_D$ +11,300°. Davoll, Lythgoe, and Todd (*J.*, 1948, 967) record for the fission product from 2 : 8-dichloro-9-β-D-ribofuranosyladenine, $[M]_D$ +9,200°. In view of the length of time which the fission product in the present work was necessarily in contact with the oxidant, these values are in reasonable agreement.

Dehalogenation of the xyloside was achieved catalytically. A portion (480 mg.) in water (100 c.c.) containing N-sodium hydroxide (3·6 c.c.) together with 5% palladised barium sulphate (1 g.) was shaken with hydrogen. In 8 hours the theoretical amount (2·9 millimols.) of hydrochloric acid was liberated, and 74 c.c. of hydrogen had been absorbed; the solution was filtered and evaporated to dryness. To free the product from inorganic salts it was converted into its acetyl derivative which was dissolved in chloroform. The solution was washed with water, dried, and evaporated, and the residue deacetylated by methanolic barium methoxide. The 9-β-D-xylofuranosyladenine so obtained formed a glassy solid (220 mg., 58%), $[\alpha]_D^{20}$ −19° (*c*, 1·2 in water), which could not be obtained crystalline as such, but was converted into the *picrate*, yellow needles (from water), m. p. 210° (decomp.), $[\alpha]_D^{20}$ −43° (*c*, 0·62 in pyridine) (Found: C, 38·7; H, 3·6; N, 22·5. $C_{10}H_{13}O_4N_5.C_6H_3O_7N_3$ requires C, 38·7; H, 3·3; N, 22·6%).

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408. *The Polysaccharides of Carragheen. Part III. Confirmation of the 1 : 3-Linkage in Carrageenin, and the Isolation of* L-*Galactose Derivatives from a Resistant Fragment.*

By R. Johnston and E. G. V. Percival.

Carrageenin, after partial hydrolysis with oxalic acid, yielded a dialysable degraded polysaccharide from which 25% of the original sulphuric ester groups had been removed. 2 : 4 : 6-Trimethyl galactose, accompanied by tetramethyl galactopyranose and 2 : 6-dimethyl galactose, was produced on hydrolysing the methylated degradation product, thus supporting the previous conclusion that the principal linkage is through $C_{(1)}$ and $C_{(3)}$ with the sulphate residue on $C_{(4)}$.

On treatment of carrageenin with methanolic hydrogen chloride at room temperature a residue (15%) with a low sulphate content (1·5%) remained, whilst methylgalactosides and sodium methyl sulphate, etc., dissolved. The resistant fragment ($[\alpha]_D$ −5°) gave an acetate which on deacetylation and methylation gave a methyl derivative, among the products of hydrolysis of which were identified 2 : 3 : 4 : 6-tetramethyl and 2 : 4 : 6-trimethyl L-galactose, as well as smaller quantities of the corresponding D-galactose derivatives, 2 : 4-dimethyl D-galactose and trimethyl D-xylopyranose. Some implications of these results are discussed.

In Parts I and II of this series (*J.*, 1943, 51; 1947, 1622) the isolation of 2 : 6-dimethyl D-galactose from the methylated polysaccharides prepared from *Chondrus crispus* and *Gigartina stellata* extracts, respectively, together with the stability to alkaline hydrolysis of the sulphate residues, provided evidence that the principal linkage between D-galactose residues in carrageenin was through $C_{(1)}$ and $C_{(3)}$ with the hydroxyl group on $C_{(4)}$ esterified by sulphate. Further support for this view has now been obtained in the isolation of 2 : 4 : 6-trimethyl galactose from specimens of carrageenin which had been partly degraded by treatment with dilute oxalic acid and then methylated and hydrolysed. The degraded carrageenin which was soluble in 80% ethanol–water and was of a sufficiently small particle size to pass through a cellophane membrane by dialysis, had lost 25% of its original bound sulphate. After methylation, hydrolysis, and glycoside formation followed by continuous extraction with suitable solvents, mixtures of methylglycosides of tetramethyl D-galactopyranose (*ca.* 12%) and 2 : 4 : 6-trimethyl D-galactose (*ca.* 18%) were separated from 2 : 6-dimethyl methylgalactosides which remained in the aqueous solution. Although the free sugars isolated on hydrolysis were homogeneous when examined on the paper chromatogram and readily gave crystalline aniline derivatives several recrystallisations were necessary before pure crystalline products were obtained. In the light of the results which follow, it seems highly probable that there was some contamination by the corresponding enantiomorphs. The main conclusion to be drawn from these experiments, however, is that the 2 : 4 : 6-trimethyl galactose is derived from units linked through $C_{(3)}$, and that these residues formerly carried a sulphate group on $C_{(4)}$, since the main product of the hydrolysis of methylated carrageenin is 2 : 6-dimethyl galactose.

Carrageenin cannot be represented simply by a chain of galactose units linked through the 1 : 3-positions. When the polysaccharide is shaken with 1% methanolic hydrogen chloride at room temperature the greater part dissolves with the production of methylgalactosides and salts of methylsulphuric acid. An insoluble residue (*ca.* 15%) remains, however, which is practically devoid of sulphate and, in contradistinction to the original carrageenin ($[\alpha]_D$ +63°) has a slightly negative rotation ($[\alpha]_D$ −5°) which is enhanced in magnitude in its acetyl and methyl derivatives. Hydrolysis followed by chromatographic analysis showed galactose (70%) to be the principal constituent of this resistant material but xylose (*ca.* 7%) was present also, the amount being in reasonable agreement with the pentose content of the original polysaccharide (Part I, *loc. cit.*). Methylation proved to be difficult, and the product of the highest methoxyl content (OMe, 40·9%) was prepared from a specimen of the acetate by deacetylation and methylation. Hydrolysis of this methylated substance and analysis by quantitative paper chromatography gave tetramethyl galactopyranose (1 part), 2 : 4 : 6-trimethyl galactose (2·3 parts), and 2 : 4-dimethyl galactose (1·5 parts). Separation on a powdered cellulose column (Hough, Jones, and Wadman, *J.*, 1949, 2511) gave crystalline trimethyl D-xylopyranose (*ca.* 0·4 part), tetramethyl galactopyranose (*ca.* 1 part), 2 : 4 : 6-trimethyl galactose (*ca.* 2·8 parts), 2 : 4-dimethyl galactose (*ca.* 1·3 parts), and momomethyl galactoses (*ca.* 1 part). In view of the scale of this experiment it is not claimed that the relative proportions indicated are more than rough approximations. The figures for the last three sugars listed are indeed almost certainly too low since certain mixed fractions containing these were not analysed. The trimethyl xylopyranose may have been derived from a contaminating xylan such as that found

in the red seaweed, *Rhodymenia palmata* (Barry and Dillon, *Nature*, 1940, **146**, 620), and it cannot be assumed that a D-xylopyranose end-group is present in the galactan.

The tetramethyl galactopyranose had $[\alpha]_D$ −43° and gave a crystalline aniline derivative, m. p. 185—187° depressed to 175° on admixture with tetramethyl D-galactopyranose anilide. On recrystallisation almost pure tetramethyl L-galactopyranose anilide was obtained, and from the specific rotation of the original syrup it is concluded that *ca.* 70% of the tetramethyl galactose in the mixture was the L-form.

The trimethyl galactose which was identical with 2 : 4 : 6-trimethyl galactose on the paper chromatogram gave a crystalline aniline derivative, m. p. 165°, from which with some difficulty a specimen, m. p. 174°, was obtained which was principally 2 : 4 : 6-trimethyl L-galactose anilide. The original sugar failed to crystallise, unlike the readily crystallisable 2 : 4 : 6-trimethyl D-galactose, and from the observed specific rotation ($[\alpha]_D$ −43°) it was presumed to contain *ca.* 75% of the L-isomer.

The dimethyl galactose gave a good yield of 2 : 4-dimethyl D-galactose anilide, and no evidence for the presence of the L-isomer was found in this case.

The list of constituents in the mixture of methylated sugars obtained on hydrolysing the resistant fragment of carragheenin, after methylation, must be revised as follows; the relative proportions indicated being rough approximations only. Trimethyl D-xylopyranose (1 part), tetramethyl D-galactopyranose (1 part), 2 : 4 : 6-trimethyl D-galactose (2 parts), 2 : 4-dimethyl D-galactose (4 parts), tetramethyl L-galactopyranose (2 parts), and 2 : 4 : 6-trimethyl L-galactose (6 parts). The monomethyl galactoses were probably a mixture of 2-methyl and 4-methyl galactose but no structural significance is attached to this fraction at present in view of the possibilities of incomplete methylation and of demethylation during hydrolysis. Carragheenin could, therefore, be depicted as a complex structure based on a resistant backbone relatively rich in L-galactose residues, branched, as witness the high proportion of terminal groups, the branching-points being D-galactose residues linked through $C_{(1)}$, $C_{(2)}$ and $C_{(4)}$, and with intermediate D- and L-galactopyranose units linked through $C_{(1)}$ and $C_{(3)}$. To this backbone which constitutes about one-sixth of the whole molecule, chains of 1 : 3-linked D-galactose units having sulphate groups on $C_{(4)}$ would be attached to those residues appearing as terminal groups in the exposed resistant skeleton. There is indeed no reason to deny that both D- and L-galactose units could co-exist in the same polysaccharide as in the snail galactogen of Bell and Baldwin (*J.*, 1941, 125), and it may be recalled that D- and L-galactose derivatives have been isolated on several occasions from seaweed polysaccharides, *e.g.*, from *Porphyra laciniata* (Tollens, *Ber.*, 1901, **34**, 1422), *Porphyra tenera* (Miwa, *Jap. J. Bot.*, 1940, **11**, 42), and agar (Jones and Peat, *J.*, 1942, 225; Forbes and Percival, *ibid.*, p. 1844). The possibility still exists, however, that carragheenin is a mixture, and that the resistant residue is a separate polysaccharide; we have not yet succeeded in giving a definite answer to this question.

Experimental.

The Partial Hydrolysis of Carragheenin.—The *Chondrus crispus* polysaccharide (hot extract) prepared as described in Part I (*loc. cit.*) (9 g.) in oxalic acid (400 c.c.; 0·1N.) containing potassium oxalate (0·05M.) was heated at 100° for 4 hours in an atmosphere of nitrogen. On being poured into ethanol (800 c.c.) a precipitate (0·8 g.) was obtained which was removed, and no further precipitate appeared on dilution with a further quantity of ethanol (2 l.). After neutralisation with barium carbonate, filtration, and concentration at 30°/15 mm., a glass (7·8 g.) was obtained which contained 5% of free galactose (estimated as the phenylmethylhydrazone). When the glass, dissolved in water, was dialysed for five days, the water being changed daily against distilled water, using a cellophane membrane, and all the solutions evaporated, 81% of the material was recovered. Free sulphate ions were absent; $[\alpha]_D^{20}$ +22·5 (*c*, 1·8 in water) (Found: SO_4, 17·9%).

Methylation Experiments.—The glass (7·3 g.) was methylated as described for maltose (Haworth and Leitch, *J.*, 1919, 809), with methyl sulphate (114 c.c.) and sodium hydroxide (111 c.c.; 30%), the final reaction mixture being just alkaline. Extraction with chloroform gave a brown syrup (0·7 g.) which was chiefly tetramethyl methylgalactopyranoside, as shown by hydrolysis and analysis on the paper chromatogram (this substance arose from the free galactose which contaminated the starting material). The extracted solution was then poured into ethanol (4 volumes) and the precipitated salts removed by filtration after being kept overnight. The solution was then evaporated to dryness, and the product dried with alcohol–benzene and extracted with ethanol to give a yellow glass (5 g.) (Found: OMe, 23·2%).

This product was treated with thallous ethoxide (15 g.) in ethanol–benzene (1 : 1), and the thallium complex precipitated on "Hyflo" Super Cel by evaporation at 40°/15 mm. The powdered material was boiled with methyl iodide (150 g.) until no longer alkaline. After filtration the residue was exhaustively extracted with acetone, and the filtrate and washings on evaporation gave a brown glass (3·5 g.); $[\alpha]_D^{20}$ +21° (*c*, 1·0 in chloroform) (Found: OMe, 41·6; SO_4, 20·4%).

Hydrolysis and Glycoside Formation.—The methylated glass (3 g.) in oxalic acid (120 c.c.; 0·5N.) was hydrolysed at 100° for 18 hours in the presence of chloroform (20 c.c.) to prevent undue access of air. Neutralisation with barium carbonate, filtration, and evaporation gave a product which was boiled with methanolic hydrogen chloride (70 c.c.; 3%). The brown solution was then neutralised with silver carbonate and evaporated to give a brown syrup (2·5 g.).

Fractionation of the Mixture of Glycosides.—The syrup (2·5 g.) in water (30 c.c.) together with a little barium carbonate was extracted with light petroleum (b. p. 40—60°) in a continuous extractor (Brown and Jones, *J.*, 1947, 1344) to give, after 19 hours 0·48 g., and after 24 hours a further 0·03 g. of syrup; these products were combined (1). The solution was then transferred to the apparatus for extraction by solvents heavier than water, and extracted with chloroform to give (2), 1·11 g. after 46 hours, 0·02 g. only of this being extracted in the last 24 hours. The aqueous solution was evaporated to give a mixture of a syrup and inorganic material (3).

Examination of Fraction (1).—Fraction (1) was distilled at 90—95° (bath temp.)/0·01 mm. to give a liquid (0·34 g.), n_D^{18} 1·4538 (1*a*), and a smaller fraction (0·06 g.), n_D^{18} 1·4570 (1 *b*) (Found : OMe, 50·5%).

Fraction (1*a*) in sulphuric acid (50 c.c.; N.) was heated at 100° for 6 hours. After neutralisation with barium carbonate and the usual treatment a reducing product was obtained (0·3 g.); $[\alpha]_D^{18}$ +67° (*c*, 3·3 in water) (Found : OMe, 50·0. Calc. for $C_{10}H_{20}O_6$: OMe, 52·5%). This substance (0·1 g.) in ethanol (5 c.c.) was treated with aniline (0·05 g.) at 80° for 1·5 hours. On evaporation (to 3 c.c.) and cooling, there were obtained the characteristic needles of tetramethyl galactopyranose anilide, m. p. 176° depressed to 157° on admixture with 2 : 4 : 6-trimethyl D-galactose anilide (m. p. 175°), raised to 168° on admixture with tetramethyl D-galactopyranose anilide. Recrystallisation from ethanol gave a product, m. p. 168—169° not depressed on admixture with tetramethyl D-galactopyranose anilide (m. p. 193°).

Fraction (1*b*) on hydrolysis and examination on the paper chromatogram gave a spot R_G 0·67 identical with a control of 2 : 4 : 6-trimethyl galactose; a minute trace of tetramethyl galactopyranose was also detected.

Examination of Fraction (2).—Fraction (2) on distillation gave the following sub-fractions : (2*a*) (0·11 g.), b. p. 92—97° (bath temp.)/0·07 mm., n_D^{18} 1·4575 (Found : OMe, 51·0%); (2*b*) (0·33 g.), b. p. 97—107° (bath temp.)/0·01 mm., n_D^{18} 1·4602 (Found : OMe, 51·3%); (2*c*) (0·13 g.), b. p. 107—140° (bath temp.)/0·01 mm., n_D^{18} 1·4697 (Found : OMe, 44·8%); and (2*d*) residue (0·5 g.).

Fraction (2*a*) in sulphuric acid (10 c.c.; N.) for 4 hours at 100° changed from $[\alpha]_D^{18}$ +58° ⟶ +75°. Conversion into the aniline derivative gave an impure product (m. p. 130—146°, raised to 160° on being washed with ether–ethanol). The crude derivative, dissolved in light petroleum–chloroform (6 : 1), was passed through a short column of activated alumina (5 × 0·7 cm.). The first volume of eluate on evaporation gave a product (5 mg.), m. p. 172° unchanged on admixture with 2 : 4 : 6-trimethyl D-galactose anilide (m. p. 175°). The mother-liquors obtained from the recrystallisations and washing processes were evaporated and hydrolysed with sulphuric acid (0·1N.) at 100° for 3 hours, and, after neutralisation, the free sugars (0·23 g.) were extracted by using ether. Examination on the paper chromatogram by direct comparison with an authentic specimen showed 2 : 4 : 6-trimethyl galactose to be the only reducing component.

Fraction (2*b*) showed $[\alpha]_D^{17}$ +69° (*c*, 3·3 in N-sulphuric acid) after 5 hours at 100°. The isolated sugar gave an aniline derivative, m. p. 168° not depressed on admixture with 2 : 4 : 6-trimethyl D-galactose anilide but depressed to 145° on admixture with 2 : 3 : 4-trimethyl D-galactose anilide (m. p. 169°).

Fraction (2*c*) had $[\alpha]_D^{18}$ +66° (*c*, 1·3 in N-sulphuric acid) after 4 hours at 100°. Examination of the isolated sugar on the paper chromatogram showed 2 : 4 : 6-trimethyl galactose to be the only component.

The residue (2*d*) was extracted with hot water, the solution evaporated, and the syrupy residue (0·08 g.) hydrolysed and examined on the chromatogram. 2 : 6-Dimethyl galactose (R_G 0·51) and 2 : 4 : 6-trimethyl galactose (R_G 0·67) were found to be present.

Examination of Fraction (3).—This mixture on extraction with cold ethanol and evaporation of the extracts gave a pale-yellow glass (0·55 g.) (Found : OMe, 14·8%). This still contained inorganic material. Hydrolysis and examination on the paper chromatogram showed the principal sugar component to be 2 : 6-dimethyl galactose.

Isolation of a Resistant Fraction from Carraghœnin.—Dry, powdered, carraghœenin (hot extract from *Gigartina*) (9·8 g.) was shaken vigorously for 24 hours at room temperature with methanolic hydrogen chloride (920 c.c.; 1%). The residue was removed on a sintered-glass filter and washed with dry methanol (3·7 g.). This product was then purified by four further treatments with methanolic hydrogen chloride, and, after being washed with methanol, dissolved in warm water in the presence of barium carbonate and centrifuged; concentration and precipitation in ethanol gave a substance (*R*) (2·1 g.) which had $[\alpha]_D^{18}$ −5° (*c*, 1·3 in water), +19·4° after 18 hours at 100° in 0·5N-sulphuric acid [Found : SO_4, 1·5; H_2O (micro*Zerewitinow*), 9%]. Analysis of the hydrolysate by the paper chromatogram (Flood, Hirst, and Jones, *J.*, 1948, 1678) gave galactose 71 and xylose 7%.

The methanolic solution was neutralised with silver carbonate, filtered, and treated with hydrogen sulphide, the excess of which was removed by aeration; the solution was neutralised with barium carbonate, filtered, and evaporated to dryness. The non-reducing colourless glass (7·1 g.) had $[\alpha]_D^{18}$ +13°, rising to +31° on hydrolysis with sulphuric acid (0·5N.) [Found : SO_4, 28·8; OMe, 16·6; galactose (phenylmethylhydrazone) 40%].

No sugar other than galactose could be detected in the hydrolysed material, and a search for organic acids using ion-exchange resins proved abortive. Barium dimethyl disulphate was isolated by passing a solution of the glass through " Zeo-Karb H.1. " and the acid solution was then percolated through a

column of " Deacidite B." The neutral solution so obtained gave on evaporation a glass which on hydrolysis gave 72·5% galactose by quantitative chromatogram. When the " Deacidite B " column was treated with barium hydroxide (0·2N.) and the excess removed by carbon dioxide, after filtration, evaporation, and extraction with aqueous ethanol crystalline barium methyl sulphate was isolated.

The Acetylation and Methylation of the Resistant Fraction.—The substance *R* (10 g.) was acetylated by a modification of the method of Pacsu and Mullen (*J. Amer. Chem. Soc.*, 1941, **63**, 1487). After dissolution in water, addition of pyridine and dehydration by distillation with the addition of more pyridine, the product was gelatinised by addition of pyridine (240 c.c.). Acetic anhydride (190 c.c.) was then added with vigorous mechanical stirring and after being stirred overnight the mixture was heated at 60° for 30 minutes. A small quantity of insoluble gel was removed by centrifugation, and the remainder poured into ice-water and the precipitate (*A*) filtered off and washed with water. The insoluble residue did not dissolve on further acetylation at 70° and was also precipitated in ice-water (*B*). (*A*) (8·2 g.) had $[\alpha]_D^{20}$ −39° (*c*, 1·0 in acetone) (Found : Ac, 36·5). (*B*) (0·9 g.) (Found : Ac, 21·0; ash, 4%). (*A*) in chloroform (200 c.c.) was treated with light petroleum (b. p. 40—60°; 60 c.c.) to give (*a*) (1·44 g.; Ac, 36·0%); with a further 30 c.c. (*b*) 3·55 g. (Ac, 39·1%); and on evaporation (*c*) 2·24 g., $[\alpha]_D^{20}$ −56° (*c*, 2·2 in chloroform) (Found : Ac, 40·6%).

A mixture of (*b*) and (*c*) (4·5 g.) was simultaneously deacetylated and methylated as for glycogen acetate (Haworth and Percival, *J.*, 1932, 2279). The solution obtained after treatment with methyl sulphate and sodium hydroxide was extracted with chloroform, and the product obtained on evaporation of the chloroform extracts was methylated three times with methyl iodide and silver oxide to give a product (1·25 g.), $[\alpha]_D^{20}$ −34·5° (*c*, 2·0 in chloroform) (Found : OMe, 25·1%).

The aqueous solution was neutralised with acetic acid and evaporated to crystallisation. After filtration the aqueous solution was dialysed, evaporated, and remethylated with sodium hydroxide and methyl sulphate, and the product obtained by extraction with chloroform was added to the material extracted from the crystalline residue by ethanol; the mixture was methylated twice with methyl iodide and silver oxide to give further partly methylated material (0·8 g.), $[\alpha]_D^{20}$ −40° (*c*, 2·0 in chloroform) (Found : OMe, 32·2%). This product was added to that obtained by the original chloroform extraction, and the mixture remethylated with methyl sulphate and sodium hydroxide. After dialysis a glass (*X*) (1·37 g.), $[\alpha]_D^{20}$ −50° in chloroform, was obtained (Found : OMe, 40·9%).

Attempts to obtain a better yield of the methylated product by direct methylation with sodium hydroxide and methyl sulphate under nitrogen were unsuccessful.

By using the thallium method (Hirst and Jones, *J.*, 1938, 502) the polysaccharide (3 g.) on treatment with thallous hydroxide (45 c.c.; N.) gave a thallium complex (8·1 g.) which was filtered off and dried by treatment with ethanol–benzene and removal of the solvents at 25—30° (diminished pressure). The product was ground and boiled for 7 days with methyl iodide containing 10% methanol. Extraction of the neutral solid with water, after removal of methyl iodide by distillation, gave a product (2·4 g.) (Found : OMe, 17·7%). This was dissolved in dry methanol and thallium ethoxide (1·25 c.c.) in benzene (25 c.c.) was added at 0°. After filtration the solid was dried and boiled for 4 days in methyl iodide containing methanol (5%). Extraction with boiling acetone gave a pale yellow glass (*Y*) (Found : OMe, 35·3%). Five treatments with methyl iodide and silver oxide failed to increase the methoxyl content.

The Hydrolysis and Analysis of the Methylated Fragment.—The glass (*X*) (1·37 g.), in methanolic hydrogen chloride (80 c.c.; 2%), was boiled for 36 hours at 70°. After neutralisation with silver carbonate a brown syrup (1·34 g.) was obtained. This product in sulphuric acid (25 c.c.; N.) was heated at 100° for 7·5 hours in an atmosphere of nitrogen, and the solution neutralised with barium carbonate, filtered, and evaporated at 30°/15 mm. to give a golden syrup (1·11 g.). Analysis on the paper chromatogram using alkaline iodine (Chanda, *et al.*, *J.*, 1950, 1289) gave the following sugars in the approximate molecular proportions indicated : tetramethyl galactopyranose (1 part), 2 : 4 : 6-trimethyl galactose (2·4 parts), 2 : 4-dimethyl galactose (1·5 parts), as well as trimethyl xylopyranose and monomethyl galactose(s) in smaller proportion.

Separation on the cellulose column. The sugars (0·86 g.) were separated on a column of powdered cellulose (35 × 3·25 cm.) by using a 7 : 3-mixture of petroleum (b. p. 100—120°) and butanol (water saturated) (Hough, Jones, and Wadman, *loc. cit.*). Samples (*ca.* 4 c.c.) were collected at intervals of 6 minutes. After the collection of 500 tubes the column was allowed to drain, and a 4 : 1-mixture of butanol (water-saturated) and ethanol was used for elution, the time interval being adjusted gradually to 24 minutes. The contents of every tenth tube were evaporated and examined on the paper chromatogram, the papers being developed with saturated aniline oxalate solution. The following fractions were isolated :

I (161—220), R_G 0·95; II (321—340), R_G 0·895; III (371—500), R_G 0·88; IV (521—593), R_G 0·79; V (594—600), R_G 0·79, 0·67; VI (601—620), R_G 0·67; VII (621—639), R_G 0·67, 0·60, 0·52, 0·44; VIII (640—668), R_G 0·44; IX (669—690), R_G 0·44, 0·19; X (691—721), R_G 0·19. Tubes 722—786 showed the presence of traces of xylose and galactose.

Examination of fractions. Fraction I (0·034 g.), $[\alpha]_D^{20}$ +18° (*c*, 3·0 in water), crystallised completely; it had m. p. 89° not depressed on admixture with authentic trimethyl D-xylopyranose with which it was identical on the chromatogram.

Fraction II (0·01 g.) was a waxy substance which, on extraction with water, gave no spot on the chromatogram.

Fraction III (0·087 g.), $[\alpha]_D^{20}$ −43° (Found : OMe, 50·5. Calc. for $C_{10}H_{20}O_6$: OMe, 52·5%). It was chromatographically identical with tetramethyl galactopyranose. The aniline derivative had m. p. 185—187° depressed to 174° with tetramethyl D-galactopyranose anilide. On recrystallisation the product had $[\alpha]_D^{20}$ +70° (*c*, 0·4 in acetone), m. p. 192—193° depressed to 173—176° on admixture with

tetramethyl D-galactopyranose anilide ($[\alpha]_D$ −80° in acetone) (Found : N, 4·6. Calc. for $C_{18}H_{31}O_6N$: N, 4·5%).

Fraction IV (0·036 g.), $[\alpha]_D^{20}$ +47°, was not identified.

Fraction VI (0·226 g.), $[\alpha]_D^{20}$ −43° (*c*, 2·2 in water) (Found : OMe, 40·3. Calc. for $C_9H_{18}O_4$: OMe, 41·9%). It was chromatographically identical with 2 : 4 : 6-trimethyl galactose. This syrup (0·03 g.) gave an aniline derivative (0·012 g.), m. p. 165° [$[\alpha]_D^{20}$ +49° (initial value ; *c*, 0·5 in acetone)] raised to 174° by recrystallisation from ethanol and depressed to 167° on admixture with 2 : 4 : 6-trimethyl D-galactose anilide. The recrystallised aniline derivative had $[\alpha]_D^{20}$ +65° (initial) changing to −20° (1 day) (*c*, 1·1 in acetone); 2 : 4 : 6-trimethyl D-galactose anilide has $[\alpha]_D$ −92° falling to +38° (22 hours) (Hirst and Jones, *J.*, 1939, 1482), so that the aniline derivative obtained from fraction VI contains 80—85% of the L-isomer (Found : N, 5·0; OMe, 29·5. Calc. for $C_{15}H_{23}O_5N$: N, 4·7; OMe, 31·3%).

Fraction VIII (0·103 g.), $[\alpha]_D^{20}$ +47·6 (*c*, 1·0 in water) (Found : OMe, 29·1. Calc. for $C_8H_{16}O_4$: OMe, 29·9%). The syrup (0·034 g.) gave an aniline derivative which separated from the hot ethanolic solution after 30 minutes. Cooling, filtration, and recrystallisation from ethanol gave prisms (0·019 g.), m. p. 208° not depressed on admixture with authentic 2 : 4-dimethyl D-galactose anilide (Found : N, 5·2; OMe, 20·5. Calc. for $C_{14}H_{21}O_5N$: N, 5·0; OMe, 21·9%).

Fraction X (0·068 g.), $[\alpha]_D^{20}$ +42·5° (*c*, 0·7 in water), failed to give a crystalline derivative. Examination on the paper chromatogram showed the absence of 6-methyl galactose.

Fractions V, VII, and IX were mixtures, and amounted together to 0·26 g.; total recovery 0·82 g. (95%).

Examination of methylated specimen (Y). A portion of (*Y*) was hydrolysed and the methylated sugars released estimated as before by the quantitative chromatogram to give trimethyl xylopyranose (1·3 parts), tetramethyl galactopyranose (1 part), 2 : 4 : 6-trimethyl galactose (2·6 parts), dimethyl sugars (2·7 parts), and monomethyl sugars (1·2 parts). The ratio of trimethyl to tetramethyl galactose is in good agreement with that found for (*X*).

Thanks are expressed to Imperial Chemical Industries Limited and to the Earl of Moray Endowment for grants.

KING'S BUILDINGS, UNIVERSITY OF EDINBURGH. [*Received, May 3rd,* 1950.]

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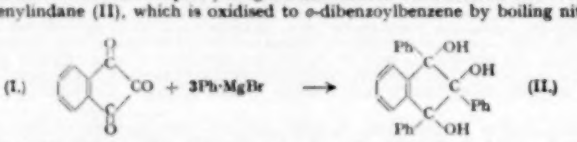
409. *Studies on Indene Derivatives. Part VII. New Reactions of Triketoindane and Experiments with Hydrindantin and Related Compounds.*

By RADWAN MOUBASHER, WILLIAM AWAD, MOUSTAFA IBRAHIM, and ABDEL MOGID OTHMAN.

New derivatives of triketoindane have been prepared. The thermal decomposition of bis-(2-hydroxy-1 : 3-diketoindan-2-yl) (V) yields bis-(3-hydroxy-1-ketoinden-2-yl) (VI) and phthalic anhydride. The nature of the deep blue colour obtained from (I) $+H_2O$, (V) $+2H_2O$, and 2 : 2-dihydroxyperinaphthane-1 : 3-dione by strong alkali is discussed; in the last case, after acidification, 2-hydroxyperinaphthane-1 : 3-dione is obtained in good yield.

CONTINUING the work of one of us (R. M.) on the properties of indane-1 : 2 : 3-trione (I), we have investigated its reaction with phenylmagnesium bromide * and isolated 1 : 2 : 3-trihydroxy-1 : 2 : 3-triphenylindane (II), which is oxidised to *o*-dibenzoylbenzene by boiling nitric acid.

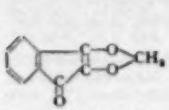


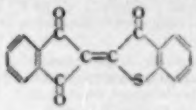
As with diphenyl triketone (Schönberg and Moubasher, *J.*, 1941, 348), a five-membered ring is formed when the indanetrione † (I) or the analogous perinaphthindanetrione (VII — H_2O) is treated with diazomethane, giving 2 : 3-methylenedioxyindan-1-one (III) and 2 : 3-methylenedioxyperinaphthinden-1-one respectively, which with boiling alcoholic hydrochloric acid yield bis-(3-hydroxy-1-ketoinden-2-yl) (VI) and 2 : 3-dihydroxyperinaphthinden-2-one (the enolic form of VIII) respectively.

Thionaphthan-3-one and (I) give the violet red 2-(3-ketothionaphthen-2-ylidene)indane-1 : 3-dione (IV), but attempted condensation with indane-1 : 3-dione gave only (VI).

* These experiments were performed by Moustafa Ibrahim.
† These experiments were performed by William Awad.

The anhydrous substance (V) (Schönberg *et al.*, *J.*, 1950, 376), when heated at 270° in a vacuum or in carbon dioxide, gives (VI) and phthalic anhydride. When (V) is exposed to


(III.)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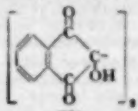
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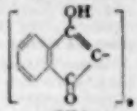
(VI.)

sunlight with benzoquinone in benzene solution, dehydrogenation takes place, followed by fission, with the formation of the trione (I); this behaviour is frequently met with in pinacols (Schönberg and Mustafa, *J.*, 1944, 67).

The action of strong alkali on hydrindantin or (V) leads to the formation of a blue colour owing to formation of the alkali salt of the enolic form of 2-hydroxyindane-1 : 3-dione (Ruhemann, *J.*, 1911, **99**, 1306). Its formation is easily explained on the basis of the formula (V + $2H_2O$) for hydrindantin (cf. the formation of benzhydrol and fluorenol by the action of the alkali on tetraphenylethylene glycol and the acetate of fluorenone-pinacol, respectively; Thörner and Zinke, *Ber.*, 1877, **10**, 1473; Klinger and Lonnes, *ibid.*, 1896, **29**, 2157). The intense blue colour which is produced when ninhydrin is treated with concentrated alkali is, according to Errera (*Chem. Centr.*, 1913, **11**, 774), also caused by formation of a salt similar in structure to (VIII). In favour of this opinion are the facts that perinaphthindane-1 : 2 : 3-trione hydrate (VII) gives with strong alkali a deep-blue solution which when acidified yields

(VII.) (VIII.)

2 : 3-dihydroxyperinaphthinden-1-one (the enolic form of VIII), and that (VIII) and benzoyl chloride yield the corresponding dibenzoate.

Experimental.

Action of Phenylmagnesium Bromide on Indane-1 : 2 : 3-trione.—The trione (Schönberg and Moubasher, *J.*, 1943, 71) (1 g.) was added to ethereal phenylmagnesium bromide (from 1 g. of magnesium and 8 g. of bromobenzene in 50 c.c. of ether), a vigorous reaction taking place. Benzene (50 c.c.) was then added, and the whole refluxed for ½ hour and left overnight. The mixture was then treated with dilute hydrochloric acid and extracted with ether, the ethereal extract dried (Na_2SO_4), filtered, and evaporated up to dryness, and the residue (2 g.) crystallised from benzene–light petroleum (1 : 3 by vol.). 1 : 2 : 3-*Trihydroxy*-1 : 2 : 3-*triphenylindane* forms colourless needles, m. p. 124—130° (Found: C, 83·6; H, 6·0. $C_{21}H_{22}O_3,C_6H_6$ requires C, 83·8; H, 5·9%). When this substance is left for few days at room temperature or dried in a vacuum, benzene of crystallisation is lost, giving the colourless anhydrous *form*, m. p. 178° (Found: C, 82·3; H, 5·8; active, H, 0·7%; *M*, 388. $C_{21}H_{22}O_3$ requires C, 82·2; H, 5·6; active H, 0·7%; *M*, 394). It is soluble in benzene or ethyl alcohol, insoluble in sodium hydroxide, and gives with concentrated sulphuric acid a yellow-orange colour.

Oxidation of 1 : 2 : 3-*Trihydroxy*-1 : 2 : 3-*triphenylindane* (II).—The triol (0·5 g.), concentrated nitric acid (10 c.c., *d* 1·42), and water (20 c.c.) were refluxed for 2 hours. A yellow oil was formed which, after cooling, solidified (0·2 g.). This was recrystallised from benzene–light petroleum giving *o*-dibenzoylbenzene as yellow needles, m. p. 147° undepressed on admixture with authentic sample.

Action of Diazomethane.—(a) *On indane-1 : 2 : 3-trione.* The trione (0·5 g.) was added to an excess of ethereal diazomethane, a vigorous reaction taking place. The mixture was left overnight in an ice-chest. The ether was removed and the brown oily mass triturated with aqueous methyl alcohol, to give a yellowish solid (0·45 g.) which crystallised from methyl alcohol. 2 : 3-*Methylenedioxyinden*-1-*one* forms pale yellow crystals, m. p. 185° (Found: C, 69·4; H, 3·9%; *M*, 166. $C_{10}H_6O_3$ requires C, 68·9; H, 3·4%; *M*, 174).

The product (0·2 g.), hot methyl alcohol (15 c.c.), and concentrated hydrochloric acid (10 c.c.) were refluxed for 6 hours. A violet crystalline deposit (0·1 g.) formed which crystallised from benzene in violet needles, m. p. 298°, and was proved to be bis(3-hydroxy-1-ketoinden-2-yl) by mixed m. p. and general properties.

(b) *On perinaphthindane-1 : 2 : 3-trione* [Moubasher and (in part) Awad, *J.*, 1949, 1137]. The trione (0·2 g.), treated with an excess of ethereal diazomethane as in (a), gave 2 : 3-*methylenedioxyperinaphthinden*-1-*one* as pale yellow crystals (from methyl alcohol), m. p. 200° (brownish-red melt) (0·18 g.) (Found: C, 74·9; H, 3·2. $C_{14}H_8O_3$ requires C, 75·0; H, 3·5%). This gives a persistent orange colour with concentrated sulphuric acid. It is insoluble in sodium hydroxide solution.

Hydrolysis, carried out as above, gave a reddish flocculent substance which crystallised from ethyl alcohol in red needles, m. p. 258°, undepressed with authentic 2 : 3-dihydroxyperinaphthinden-1-one prepared according to Errera (*loc. cit.*), and giving a blue colour with sodium hydroxide solution.

Action of Thionaphthan-3-one on Indane-1 : 2 : 3-trione.—The trione (0·5 g.) and freshly crystallised thionaphthan-3-one (0·5 g.) in dry benzene (50 c.c.) were refluxed for ½ hour. After cooling a violet deposit (0·7 g.) was filtered off and crystallised from benzene. *2-(3-Ketothionaphthan-2-ylidene)indane-1 : 3-dione* forms violet needles, m. p. 275° (decomp.) (Found: C, 69·3; H, 2·9; S, 11·4. $C_{17}H_8O_2S$ requires C, 69·8; H, 2·7; S, 11·1%). It gives an orange-red fluorescence in xylene and an intense blue-green colour with concentrated sulphuric acid.

Action of Indane-1 : 3-dione on Indane-1 : 2 : 3-trione.—The trione (0·5 g.) and the dione (0·5 g.) in glacial acetic acid (25 c.c.) were refluxed for 2 hours, and then cooled and filtered. The solid residue was extracted several times with benzene. From the benzene extract only violet crystals of (VI) were obtained (0·5 g.), m. p. 298° alone or mixed with an authentic sample.

Thermal Decomposition of Bis-(2-hydroxy-1 : 3-dihetoindan-2-yl).—The substance (1 g.) was heated for 5 minutes at 270° (bath-temp.) in a vacuum or in a stream of carbon dioxide. On the cold part of the tube, colourless crystals of phthalic anhydride were formed (0·08 g.) (m. p. 130° alone or mixed with an authentic sample; fluorescein test positive). A residue of (VI) (0·5 g.) remained which, crystallised from benzene, had m. p. 298°, undepressed on admixture with an authentic sample (colours with concentrated sulphuric acid and with sodium hydroxide solution).

Photo-reaction of p-Benzoquinone and Bis-(2-hydroxy-1 : 3-dihetoindan-2-yl).—The bisindanyl compound (1 g.), suspended in dry benzene (30 c.c.) containing *p*-benzoquinone (5 g.), in a Monax tube filled with carbon dioxide, was exposed to sunlight for 7 days (May). The black solid quinone separated out. The mixture was filtered and the solid treated with hot water and collected. The aqueous filtrate was extracted several times with ether (5-c.c. portions). The dried ethereal extracts were evaporated, to give ninhydrin as colourless crystals (0·1 g.), becoming red at 139° and melting at 260° to a green melt, undepressed by admixture with an authentic specimen. It gave the characteristic blue colour with concentrated sodium hydroxide solution.

Action of Alkali.—(a) *Perinaphthindane-1 : 2 : 3-trione hydrate.* The substance (0·1 g.) was suspended in distilled water (5 c.c.), and sodium hydroxide (10%; 1 c.c.) was added, an intense blue colour developing; benzoyl chloride (10 c.c.) was added immediately and the reaction mixture shaken vigorously with cooling for 1 minute, thereupon becoming yellow. The whole was added to cold water; a yellow precipitate was filtered off (0·1 g.) and recrystallised from benzene or dilute acetic acid in yellow green prisms, m. p. 215°, undepressed on admixture with an authentic sample of 2 : 3-dibenzoyloxyperinaphthinden-1-one (Errera, *loc. cit.*).

When the experiment was carried out without the addition of benzoyl chloride, acidification with hydrochloric acid after the formation of the blue colour gave 2 : 3-dihydroxyperinaphthinden-1-one (70%) which crystallised from ethyl alcohol in red needles, m. p. 258° undepressed on admixture with authentic sample.

(b) *Ninhydrin.* To ninhydrin (0·1 g.) in the minimum amount of water were added a few c.c. of aqueous sodium hydroxide. A blue colour was formed. The mixture was acidified with concentrated hydrochloric acid and kept for 24 hours, whereupon hydrindantin (0·02 gr.) crystallised, having m. p. 220° (decomp.) alone or mixed with an authentic sample.

(c) *Hydrindantin.* Hydrindantin (0·1 g.) was triturated with aqueous sodium hydroxide (10%; 10 c.c.). A violet colour developed. The mixture was acidified and kept for 24 hours, hydrindantin (0·15 g.), identified as above, separating.

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410. *Alkenylation by Use of Lithium Alkenyls. Part I. The Condensation of* iso*Butenyl-lithium with Benzaldehyde and Acetophenone, and the Oxotropic Rearrangement of the Resulting Carbinols. (Studies in Molecular Rearrangement. Part III.)**

By E. A. BRAUDE and C. J. TIMMONS.

This series of papers describes the preparation and some of the reactions and synthetic applications of a hitherto almost unknown class of reagents, the alk-1-enyl-lithium derivatives (cf. Braude, Coles, and Timmons, *Nature*, 1950, **166**, 58).

Highly purified *iso*butenyl bromide (I) with lithium in ether readily gives *isobutenyl-lithium* (II) and 2 : 5-dimethylhexa-2 : 4-diene (III). Carboxylation of *iso*butenyl-lithium affords β-methylcrotonic acid and phorone. Condensation of *iso*butenyl-lithium with benzaldehyde and acetophenone yields the *iso*butenylcarbinols (VI and VIII), which on treatment with dilute acids readily undergo the expected oxotropic rearrangements to the conjugated styryl derivatives (VII and IX).

α-Methylstyryldimethylcarbinol (IX) exhibits anomalous ultra-violet light absorption properties which are explained in terms of steric interference between the α- and γ-substituents.

ONE of the limitations to the manifold synthetic applications of Grignard reagents arises from the well-known fact that alkenyl halides containing a halogen atom adjacent to an ethylenic

* Patent applications cover the subject matter of this and the following three papers.

bond are very unreactive towards magnesium and give the organo-magnesium derivatives only with great difficulty. The sole known exceptions to this rule are 2-arylvinyl bromides such as β-bromostyrene (Tiffeneau, *Compt. rend.*, **1902**, **135**, 1346; Rupe and Proske, *Ber.*, **1910**, **43**, 1231; Meyer, *Ber.*, **1922**, **55**, 817; Ziegler *et al.*, *Ber.*, **1924**, **57**, 1986; **1925**, **58**, 359; *Annalen*, **1923**, **434**, 75; **1925**, **443**, 167; Hurd and Webb, *J. Amer. Chem. Soc.*, **1927**, **49**, 546; Lüttringhaus, *Ber.*, **1934**, **67**, 1602; Wright, *J. Org. Chem.*, **1936**, **1**, 457; Koelsch and Rosewald, *J. Amer. Chem. Soc.*, **1937**, **59**, 2166; Willstaedt, *Svensk Kem. Tidskr.*, **1941**, **53**, 416; Bergmann *et al.*, *J. Amer. Chem. Soc.*, **1949**, **71**, 2968). Vinyl bromide has been claimed to react with 2-chloroprop-1-ene in the presence of magnesium to give isoprene and butadiene (Austerweil, G.P. 245,180; *Chem. Zentr.*, **1912**, I, 1267), a reaction which presumably involves an alkenylmagnesium halide as intermediate, but according to Krestinsky (*Ber.*, **1922**, **55**, 2773) vinyl bromide itself undergoes dehydrobromination to acetylene on treatment with activated magnesium. The only successful attempts to employ aliphatic-substituted vinyl bromides in Grignard condensations are those reported by Krestinsky (*ibid.*, pp. 2754, 2762, 2770) who treated *iso*butenyl (2 : 2-dimethylvinyl) bromide (I) and 1 : 2 : 2-trimethylvinyl bromide with benzaldehyde and other aldehydes in the presence of activated magnesium and obtained, amongst other products, small yields of the expected unsaturated carbinols. In our hands, appreciable reaction between *iso*butenyl bromide and magnesium could only be induced in the presence of methyl bromide, and the yields of condensation products with aldehydes or ketones were only of the order of 10%. Mousseron and his co-workers (*Bull. Soc. chim.*, **1947**, [v], **14**, 81) have reported the formation and the carboxylation in "poor" yields of the magnesium derivative of 1-chloro-2-methyl*cyclo*hexene, but neither 1-chloro*cyclo*hexene (Braude and Coles, *J.*, 1950, 2014) nor a number of other methyl-substituted homologues (Braude, Bruun, and Weedon, forthcoming paper) react appreciably with magnesium under the usual conditions. Very recently, van Dorp and Arens (Dutch P. 62,738; *Chem. Abstr.*, **1949**, 5417) have described the condensation, in unstated yields, of 2-ethoxyvinyl bromide with a C_{19} ketone in the presence of activated magnesium.

It thus appears that, whereas the use of Grignard reagents provides general methods of alkylation, arylation, and alkynylation (the Grignard derivative being prepared in the last case from the acetylenic component containing a free ethynyl grouping and an alkylmagnesium halide), alkenylation cannot generally be effected in this way, or only with great difficulty. To some extent this limitation can be overcome by alkynylation followed by semihydrogenation to give the ethylenic derivative, a method which has been extensively developed within recent years in this and other laboratories (cf. Campbell and Campbell, *Chem. Reviews*, **1942**, **31**, 77; Heilbron, Jones, *et al.*, *J.*, **1945**, 84 and later papers; Nazarov *et al.*, *Bull. Acad. Sci. U.R.S.S., Cl. Sci. chim.*, **1946**, 305, and later papers). However, semihydrogenation of the acetylenic intermediate is not always easy to achieve, especially with polyfunctional compounds, and its application is limited to the introduction of vinyl and mono-2-substituted vinyl groups.

Morton and his collaborators (*J. Amer. Chem. Soc.*, **1947**, **69**, 160, 1675; U.S.P. 2,454,082) have studied the metalation of olefins with amylsodium. With propene and the butenes, mono-metalation was found to take place almost exclusively in the allyl position, but in the case of pent-1-ene a mixture of about 20% of pent-1-enyl- and 60% of pent-3-enylsodium appeared to be formed, as judged by the proportion of αβ- and βγ-ethylenic acids obtained on carboxylation. The applicability of this method to α-alkenylation is thus evidently rather limited.

The present work originated in the desire to employ α-alkenyl organo-metallic derivatives for the synthesis of various ethylenic systems not easily accessible by the conventional routes. The difficulty of preparing Grignard reagents of this type, together with certain additional complicating factors subsequently encountered in some of their reactions (Braude and Timmons, forthcoming paper), directed our attention to the possibility of obtaining the corresponding lithium derivatives, since lithium often reacts more readily than magnesium with alkyl and aryl halides (cf. Gilman, Zoellner, and Selby, *J. Amer. Chem. Soc.*, **1932**, **54**, 1957; **1933**, **55**, 1252). The literature concerning lithium alkenyls was not encouraging; the only example previously described, styryl-lithium, is formed in no better yield than the corresponding Grignard derivative (Wright, *loc. cit.*), and attempts to metalate vinyl bromide with phenyl- or butyl-lithium result in complete dehydrohalogenation (Wittig and Harborth, *Ber.*, **1944**, **77**, *B*, 306; Gilman and Haubein, *J. Amer. Chem. Soc.*, **1945**, **67**, 1420). *cyclo*Hex-1-enyl-lithium has been postulated as an intermediate in the formation of 1-phenyl*cyclo*hexene from 1-chloro*cyclo*hexene and phenyl-lithium (Wittig and Harborth, *loc. cit.*), but it appears at least equally likely that a

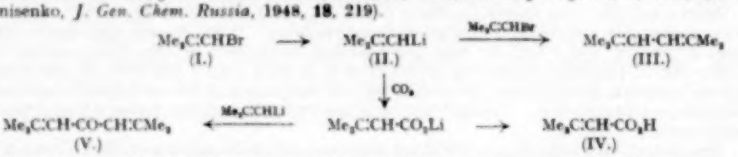
direct coupling reaction is involved (cf. Kharasch, Lewis, and Reynolds, *J. Amer. Chem. Soc.*, **1943**, **65**, 496).

We have found that lithium derivatives can readily be obtained in good yields from a variety of alk-1-enyl halides by direct reaction with metallic lithium in an anhydrous solvent, preferably ether, provided that the necessary attention is paid to the purity of the reagents employed. The preparation and some reactions of *iso*butenyl- and *cyclo*hexenyl-lithium are described in this and the following three papers. Studies of other lithium alkenyls and their synthetic applications will be reported subsequently.

***Formation and Carboxylation of* isoButenyl-lithium.**—*iso*Butenyl bromide was chosen as a test case in the present work because it gives at least small yields of the Grignard derivative under suitable conditions and cannot easily undergo dehydrobromination. The bromide was prepared by treating 1 : 2-dibromo*iso*butane with aqueous-alcoholic potassium hydroxide (Krestinsky, *loc. cit.*); the yield could not be improved beyond 30%, but various other dehydrobrominating agents were even less satisfactory. The twice-fractionated bromide reacted readily with lithium in dry ether. Treating the resulting solution with an excess of solid carbon dioxide gave 2 : 5-dimethylhexa-2 : 4-diene (III), β-methylcrotonic acid (IV), and phorone (V), in an overall yield of nearly 60%. None of the corresponding unconjugated derivatives was isolated, showing that the formation of the lithium alkenyl is not accompanied by migration of the ethylenic double bond.

There is considerable evidence that Wurtz reactions with alkali metals involve the organometallic derivatives as intermediates (cf. Ziegler and Colonius, *Annalen*, 1930, **479**, 135; Morton and Richardson, *J. Amer. Chem. Soc.*, 1940, **62**, 123). It is thus very probable that the 2 : 5-dimethylhexa-2 : 4-diene is formed by reaction of *iso*butenyl-lithium with unchanged *iso*butenyl bromide; this assumption finds some support in the fact that the yield of other condensation products derived from *iso*butenyl-lithium is increased if the bromide and lithium are allowed to interact in the presence of a secondary component, such as benzaldehyde (see below). It is of interest that little or no 2 : 5-dimethylhexa-2 : 4-diene is produced in the reaction between *iso*butenyl bromide and magnesium (Krestinsky, *loc. cit.*), whereas the bromide reacts with sodium in benzene (Prévost, *Compt. rend.*, 1927, **184**, 1460; *Ann. Chim.*, 1928, **10**, 422) or, more rapidly, in ether to give the diene as the main product. This implies, in agreement with general experience, that the reactivity of the organo-metallic derivatives towards the bromide increases in the sequence RMgBr < RLi < RNa.

The formation of phorone must be due to the reaction of lithium β-methylcrotonate, the first carboxylation product, with a second molecule of *iso*butenyl-lithium; the proportion of β-methylcrotonic acid obtained is increased, and that of phorone reduced, if the effective concentration of carbon dioxide is increased by adding the alkenyl-lithium solution to solid carbon dioxide instead of *vice versa*. The formation of ketones in the carboxylation of both magnesium and lithium organic compounds has previously been observed in a number of cases (Gilman and van Ess, *J. Amer. Chem. Soc.*, 1933, **55**, 1258; Meals, *J. Org. Chem.*, 1944, **9**, 211; Denisenko, *J. Gen. Chem. Russia*, 1948, **18**, 219).



***Condensation of* isoButenyl-lithium with Benzaldehyde or Acetophenone.**—The reaction of benzaldehyde or acetophenone with ethereal *iso*butenyl-lithium furnished the expected carbinols (VI and VIII) in about 30% yield (based on *iso*butenyl bromide), together with 2 : 5-dimethylhexa-2 : 4-diene as before. In one experiment, the formation of *iso*butenyl-lithium was allowed to proceed in the presence of benzaldehyde; the yield of phenyl*iso*butenylcarbinol (VI) was substantially the same, but a 20% yield of 1-phenyl-3-methylbuta-1 : 3-diene, a dehydration product of the carbinol, was also obtained.

The structure of phenyl*iso*butenylcarbinol (VI) was proved by hydrogenation, with platinum oxide as catalyst, to give phenyl*iso*butylcarbinol which was oxidised to *iso*valerophenone. The carbinol obtained from *iso*butenyl-lithium and acetophenone was identical in physical properties with phenylmethyl*iso*butenylcarbinol (VIII) prepared by the condensation of phenylmagnesium bromide with mesityl oxide (Ravier, *Compt. rend.*, 1934, **198**, 1786) and absorbed 1 mole of hydrogen on hydrogenation over platinum oxide to give phenylmethyl*iso*butylcarbinol.

Oxotropic Rearrangements of Phenylisobutenyl- and Phenylmethylisobutenyl-carbinol.—On treatment with dilute hydrochloric acid in aqueous dioxan, phenyl*iso*butenylcarbinol was readily isomerised to styryldimethylcarbinol (VII), identical with a sample prepared from benzylideneacetone and methylmagnesium bromide (Klages, *Ber.*, 1906, **39**, 2592). This

$$\text{Ph·CHO} \xrightarrow{\text{Me}_2\text{C:CHLi}} \underset{\text{(VI.)}}{\text{Ph·CH(OH)·CH:CMe}_2} \xrightarrow{\text{H}^+} \underset{\text{(VII.)}}{\text{Ph·CH:CH·CMe}_2\text{·OH}}$$

oxotropic rearrangement is in all respects analogous to the isomerisation of the lower homologues, phenylvinylcarbinol and phenylpropenylcarbinol, to cinnamyl alcohol and styrylmethylcarbinol, respectively (Braude, Jones, and Stern, *J.*, 1946, 396).

The corresponding rearrangement of phenylmethyl*iso*butenylcarbinol presents some unusual features. Whereas side-chain methyl substituents usually increase the ease of isomerisation (Braude and Jones, *J.*, 1946, 122, 128; Braude, Jones, and Stern, *loc. cit.*), phenylmethyl*iso*butenylcarbinol was found to rearrange considerably more slowly than phenyl*iso*butenylcarbinol under the same conditions, in aqueous dioxan containing hydrochloric acid. (Detailed kinetic studies of the rearrangement are in progress and will be reported in due course.) The rearranged isomer, 4-phenyl-2-methylpent-3-en-2-ol (IX), was also obtained on shaking (VIII) with 5% aqueous sulphuric acid, but the rearrangement under heterogeneous conditions was accompanied by some dehydration to 4-phenyl-2-methylpenta-1 : 3-diene (X), which was also obtained, though in an impure state, by distilling the rearranged carbinol (IX) from potassium hydrogen sulphate. It is of interest that Klages (*Ber.*, 1904, **37**, 2301), on decomposing the Grignard

$$\text{Ph·CO Me} \xrightarrow{\text{Me}_2\text{C:CHLi}} \underset{\text{(VIII.)}}{\text{Ph·CMe(OH)·CH:CMe}_2} \xrightarrow{\text{H}^+} \underset{\text{(IX.)}}{\text{Ph·CMe:CH·CMe}_2\text{·OH}} \longrightarrow \underset{\text{(X.)}}{\text{Ph·CMe:CH·CMe:CH}_2}$$

complex from phenylmagnesium bromide and mesityl oxide with sulphuric acid, obtained, instead of (IX) or (X), an isomeric hydrocarbon, $C_{12}H_{14}$, which, owing to its low refractive index (n_D^{20} 1·5236), was formulated as 1-phenyl-1 : 3 : 3-trimethylallene. No product of this nature was isolated in the present work.

The structure of (IX) was established by an alternative synthesis from ethyl β-methylcinnamate and methylmagnesium bromide and by the catalytic hydrogenation of both samples to 4-phenyl-2-methylpentan-2-ol, characterised as the 3 : 5-dinitrobenzoate.

The alcohol (IX) exhibits somewhat anomalous physical properties. Whereas the three lower homologues, cinnamyl alcohol, styrylmethyl- and styryldimethyl-carbinol all have melting points above 30°, α-methylstyryldimethylcarbinol (IX) could not be obtained solid at room temperature. Moreover, its ultra-violet light absorption properties differ considerably from those of its lower homologues (see Table). The other styrylmethylcarbinols uniformly show a

Ultra-violet light absorption properties of styryl and α-methylated styryl derivatives.

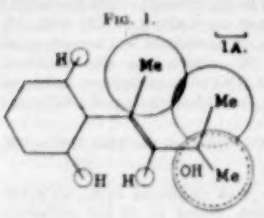
	$\lambda_{max.}$, A.*	$\varepsilon_{max.}$			$\lambda_{max.}$, A.*	$\varepsilon_{max.}$	
Ph·CH=CH$_2$	2440	12,000	[1]	Ph·CH=CH·CO$_2$Me	2710	26,000	[3]
			[3]		2800	26,000	
Ph·CMe=CH$_2$	2440	12,400					
	2500	11,200	[1]	Ph·CMe=CH·CO$_2$Et	2650	17,000	[3]
Ph·CH=CHMe	2460	12,000					
			[3]	Ph·CH=CH·CMe=CH$_2$	2730	20,200 †	[3]
Ph·CH=CH·CH$_2$·OH	2480	19,000			2790	20,200	
	2510	19,500	[2]		*2910*	13,000	
Ph·CH=CH·CHMe·OH	2480	19,000					
	2510	19,500	[2]	Ph·CMe=CH·CMe=CH$_2$	2510	11,000 †	[3]
Ph·CH=CH·CMe$_2$·OH	2510	17,300			2580	12,000	
	2560	16,300			2660	11,000	
Ph·CMe=CH·CMe$_2$·OH	2420	11,500	[2]		2760	9,000	
	2480	11,500					

* Principal bands, in ethanol solution. Figures in *italics* refer to inflections.
† These values are probably low, as the dienes were not completely pure.
[1] Ramart-Lucas and Amagat, *Bull. Soc. chim.*, 1932, **51**, 108, 965; 1934, **1**, 719.
[2] This paper. [3] Braude, Jones, and Stern, *J.*, 1946, 396; 1947, 1087.

main band with a maximum at 2510 A. (ε *ca.* 20,000), which is attributed to the conjugated styryl chromophore (Braude, Jones, and Stern, *J.*, 1947, 1087) but is considerably displaced

towards higher wave-lengths and intensified in comparison with that of styrene. The bathochromic and hyperchromic effects must clearly be ascribed to the $-CR_2{\cdot}OH$ substituents and are practically independent of whether R is hydrogen or methyl; moreover, since the ultraviolet absorption of α- as well as β-methylstyrene and other alkylated styrenes is practically identical with that of styrene (Ramart-Lucas and Amagat, *Bull. Soc. chim.*, 1932, **51**, 108, 965), the variochromic effects in the styrylcarbinols must be associated specifically with the $-C{=}CH{-}C(OH)-$ grouping and with electronic interaction (hyperconjugation) between the ethylenic bond and the hydroxyl group *via* the saturated carbon atom. Analogous effects are observed in benzyl alcohol, benzyl halides, and other hyperconjugated systems (Braude, *J.*, 1949, 1902), though the increase in intensity in the styrylcarbinols is unusually large. α-Methylstyryldimethylcarbinol (IX), on the other hand, exhibits absorption almost identical with that of styrene and α-methylstyrene; evidently in this case the α-methyl substituent almost completely inhibits hyperconjugation between the styryl system and the hydroxymethyl group. It is now well known that electronic interaction in conjugated systems requires the co-planarity of the different groups concerned and that appreciable deviations from co-planarity are strikingly manifested in the ultra-violet light absorption properties (for a recent discussion, see Braude, Jones, Koch, Richardson, Sondheimer, and Toogood, *J.*, 1949, 1890). A scale projection of α-methylstyryldimethylcarbinol (Fig. 1) using covalent radii which are a minimum measure of interference properties, shows that there is appreciable overlap between the α- and γ-methyl groups in a planar *trans*-configuration. (A *cis*-configuration can be ruled out in view of the very considerable steric interference which it would involve.) The steric interference in the *trans*-configuration can be relieved by twisting either end of the molecule, but the light-absorption data are best explained by assuming that it is the $-CMe_2{\cdot}OH$ group and the β-hydrogen atom which are displaced out of the plane of the ethylenic bond, and it can easily be seen that this is the accommodation which will result in the smallest loss of resonance energy. Several cases of steric inhibition of resonance in related first-order conjugated systems, *e.g.*, α-methylstilbene (Jones, *J. Amer. Chem. Soc.*, 1943, **65**, 1818; cf. Braude, *J.*, 1949, 1902), have been described, but as far as we are aware the present observations constitute the first recorded example of steric inhibition of hyperconjugation.

Fig. 1.



I A.

Anomalous ultra-violet light absorption properties are also exhibited by the other α-methylstyryl derivatives, ethyl β-methylcinnamate and 4-phenyl-2-methylpenta-1 : 3-diene (see Table). Here again, steric inhibition of resonance due to the α-methyl substituent clearly comes into play, but, as would be expected, the effects are rather larger than in the example discussed above, because the terminal groups undergoing steric displacement are unsaturated.

Experimental.

(M. p.s were determined on a Kofler block and are corrected.)

*iso*Butenyl *Bromide* (I).—*iso*Butene, generated by heating *tert.*-butanol with oxalic acid (Hurd and Spence, *J. Amer. Chem. Soc.*, 1929, **51**, 3562), was passed into an excess of bromine. The crude product, obtained in 85% yield in 2-kg. batches, was distilled to give 1 : 2-dibromo*iso*butane as a colourless oil, b. p. 152°, n_D^{20} 1·5078 (Dojarenko, *Ber.*, 1926, **59**, 2946, gives b. p. 147°/742 mm., n_D^{17} 1·5103; Winstein and Grunwald, *J. Amer. Chem. Soc.*, 1948, **70**, 836, give n_D^{25} 1·5095).

The dibromide (1800 g.) was added to a stirred, hot solution of potassium hydroxide (520 g.) in ethanol (2·5 l.) and water (200 ml.) at a rate sufficient to maintain gentle refluxing. The mixture was then heated under reflux for a further 7 hours and allowed to cool overnight. The upper layer was separated by suction through a filter-stick and added to water (15 l.). Next morning the lower layer was separated and dried ($CaCl_2$). On careful fractionation, through a 14-inch Fenski column, a middle fraction (470 g.), b. p. 91·0—91·5°, was obtained which was refractionated from a small piece of sodium to give *iso*butenyl bromide (360 g., 27%) as a colourless liquid, b. p. 91·0—91·3°, n_D^{25} 1·4603 (Farrell and Bachman, *ibid.*, 1935, **57**, 1281, give b. p. 90—91°, n_D^{20} 1·4625). On one occasion a sample of the same b. p. but with n_D^{25} 1·4490 was obtained, which gave identical derivatives on lithium condensation. Prototropic isomerism is thus unlikely, and since geometical isomerism is excluded, the difference in refractive indices remains unexplained.

Alternatively, 1 : 2-dibromo*iso*butane (890 g.) was added dropwise, with stirring, to potassium hydroxide (250 g.) and ethylene glycol (1 l.) in a three-necked copper flask immersed in an oil-bath at 120—130°. The *iso*butenyl bromide, which distilled, was collected, dried, and fractionated as above, 109 g. (30%) of pure product being obtained.

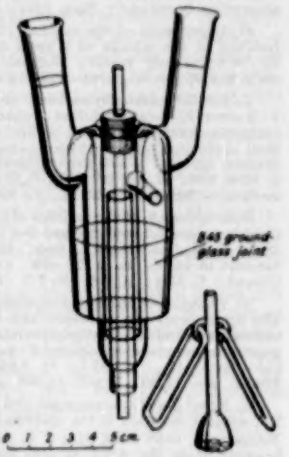
No significant yield of *iso*butenyl bromide was obtained from the attempted dehydrobromination of 1 : 2-dibromo*iso*butane with sodamide in liquid ammonia, with diethylamine or with potassium acetate

in glacial acetic acid, although Bainbridge (*J.*, **1914**, 2294) claims to have obtained a theoretical yield of the bromide by the last method.

*iso**Butenyl-lithium*** (II).—The preparation of the lithium alkenyl and subsequent reactions were carried out in wide-necked flasks fitted with the special adaptor illustrated in Fig. 2 (kindly drawn by Mr. E. S. Waight). A hollow stirrer provided with a glass wool plug at the lower end passes through the central neck which is also provided with a mercury seal. One side-neck carries an efficient reflux condenser and drying-tube; the other serves for the addition of reagents. Metallic lithium (6·9 g., 1 mol.) was cut into small pieces in a rapid stream of oxygen-free nitrogen and dropped through the side-arm into the flask, which contained sodium-dried ether (2 l., 20 mols.) and *iso*butenyl bromide (15 g.). The mixture was stirred in a slow stream of nitrogen until the reaction commenced as indicated by the appearance of a white turbidity, usually after about 45 minutes. The remainder of the bromide (total: 73 g., 0·5 mol.) in ether (150 ml.) was then added drop-wise at such a rate that the solution refluxed gently, and stirring was continued for a short time until nearly all the metal had dissolved.

For reactions in which other components are added *to* the lithium alkenyl solution, the special adaptor illustrated in Fig. 2, though convenient, is unnecessary and an ordinary three-necked flask or adaptor can be employed. For "reverse" condensations, a separating funnel was connected to the top of the stirrer by a short piece of rubber tubing, the two side-necks were closed with glass stoppers, and the lithium alkenyl solution was forced through the stirrer-tube into the funnel by applying excess nitrogen pressure; the compact design of the adaptor and short length of the stirrer-tube ensure that only a small pressure is required.

FIG. 2.



Carboxylation.—Solid carbon dioxide (200 g.) was added in small pieces to a solution of *iso*butenyl-lithium (from Li, 4·2 g.) in ether (500 ml.). When the contents of the flask had attained room temperature, water (200 ml.) was added, and the aqueous layer was acidified with hydrochloric acid. The ethereal layer was separated and extracted with aqueous sodium carbonate. On acidification of the alkaline extract, β-methylcrotonic acid (IV) (2·4 g., 7%) separated; after one crystallisation from light petroleum (b. p. 40—60°) it had m. p. 69—70°, undepressed by an authentic specimen. Distillation of the ethereal layer afforded 2 : 5-dimethylhexa-2 : 4-diene (III) (8 g., 36%), b. p. 78°/110 mm., and phorone (V) (3·2 g., 14%), b. p. 88°/17 mm., n_D^{15} 1·4968. The diene, on redistillation, had b. p. 132—133°/760 mm., m. p. 11°, n_D^{15} 1·4780 [Krestinsky (*J. Russ. Phys. Chem.*, 1920, **52**, 84; *Ber.*, 1922, **55**, 2769) gives b. p. 136°, m. p. 14·5°, n_D^{15} 1·4796]. Light absorption in ethanol: Max., 2410 A., ε = 22,500; inflections 2450 and 2500 A., ε = 21,500 and 16,500 respectively. The dihydrobromide was prepared by heating the diene with hydrogen bromide in a sealed tube at 100° for 17 hours and crystallised from light petroleum (b. p. 40—60°) in colourless needles, which sublimed to give colourless plates, m. p. 68—69° (Pogorzelsky, *Chem. Zentr.*, 1899, **I**, 773, gives m. p. 68·5—69°; Krestinsky, *loc. cit.*, gives m. p. 65°). Phorone was identified as the 2 : 4-*dinitrophenylhydrazone*, which was chromatographed on alumina from benzene solution and crystallised from methanol in red needles, m. p. 115—116°, undepressed by an authentic sample (Found: C, 56·6; H, 5·5; N, 18·3. $C_{15}H_{14}O_4N_4$ requires C, 56·6; H, 5·7; N, 17·6%); Connolly (*J.*, 1944, 339) gives m. p. 118°, and Braude and Jones (*J.*, 1945, 498) give m. p. 108°, but no analytical data are recorded.

In another experiment, in which the ethereal solution of *iso*butenyl-lithium was slowly added to excess of solid carbon dioxide, an increased yield of β-methylcrotonic acid (4·8 g., 14%) was obtained.

*Phenyl**iso**butenylcarbinol* (1-*Phenyl*-3-*methylbut*-2-*en*-1-*ol*) (VI).—(*a*) Benzaldehyde (35 g.) in ether (50 ml.) was added dropwise to a stirred ethereal solution of *iso*butenyl-lithium (from Li, 4·2 g.) at 0°. After a further hour's stirring at room temperature, an ice-cold saturated aqueous solution of ammonium chloride (35 g.) was added. The ethereal layer was separated and dried (Na_2SO_4 + a little K_2CO_3) and fractionated from a trace of potassium carbonate. A mixture of 2 : 5-dimethylhexa-2 : 4-diene and unchanged benzaldehyde distilled first, followed by phenyl*iso*butenylcarbinol (18 g., 33%), b. p. 79°/10^{-4} mm., n_D^{15} 1·5373 (Found: C, 81·3; H, 8·8. Calc. for $C_{11}H_{14}O$: C, 81·5; H, 8·7%) (Krestinsky, *Ber.*, 1922, **55**, 2770, gives b. p. 122—125°/7 mm., n_D^{20} 1·5352). Light absorption in ethanol: Max. 2590, 2640, and 2780 A., ε = 710, 670, and 360, respectively.

(*b*) A mixture of *iso*butenyl bromide (total, 58 g.) and benzaldehyde (35 g.) was added during 1 hour to lithium (4·2 g.) in ether (600 ml.) containing some *iso*butenyl bromide, after reaction had commenced as described above. Stirring was continued for a further 2 hours and the products were worked up in the usual manner to give impure 1-phenyl-3-methylbuta-1 : 3-diene (9 g., 18%), b. p. 73—76°/1 mm., n_D^{15} 1·5757 (light absorption: see Table), and phenyl*iso*butenylcarbinol (18 g., 33%), b. p. 95°/1 mm., n_D^{15} 1·5366.

Hydrogenation of phenyl*iso*butenylcarbinol (3·1 g.) in ethyl acetate (30 ml.) in the presence of platinic oxide resulted in the uptake of 1 mole of hydrogen and gave phenyl*iso*butylcarbinol (2·7 g.), b. p. 74—76°/0·05 mm., n_D^{15} 1·5072 (Grignard, *Compt. rend.*, 1900, **130**, 1323, gives b. p. 122°/9 mm., n_D^{15} 1·5080).

Oxidation of the product with potassium dichromate in sulphuric acid afforded *iso*valerophenone, identified as the 2 : 4-dinitrophenylhydrazone, m. p. 134—136°, undepressed on admixture with an authentic specimen.

Styryldimethylcarbinol (*4-Phenyl-2-methylbut-3-en-2-ol*) (VII).—A solution of phenyl*iso*butenylcarbinol (1·0 g.) in 60% aqueous dioxan containing hydrochloric acid (0·01M.) was set aside for 2 hours at room temperature. The solution was then diluted with water and extracted with ether. The ethereal extract was dried ($Na_2SO_4 + K_2CO_3$) and distilled, to give styryldimethylcarbinol (0·6 g.) which solidified on cooling and crystallised from pentane in needles, m. p. 36—37°, undepressed on admixture with an authentic specimen (Klages, *Ber.*, 1906, **39**, 2592). Light absorption in ethanol: Max. 2510, 2820, and 2910 A., ε = 17,300, 1200, and 800, respectively; inflection 2560 A., ε = 16,300.

Phenylmethylisobutenylcarbinol (*2-Phenyl-4-methylpent-3-en-2-ol*) (VIII).—An ethereal solution of *iso*butenyl-lithium (from Li, 5·6 g.) was slowly added to a stirred solution of acetophenone (35 g.) in ether (200 ml.). Stirring was continued overnight and saturated ammonium chloride solution (400 g.) was added. The products were worked up in the usual manner to give a low-boiling fraction of 2 : 5-dimethylhexa-2 : 4-diene (ca. 10 g.) and phenylmethyl*iso*butenylcarbinol (13 g., 25%), b. p. 63—64°/7 × 10^{-4} mm., n_D^{17} 1·5283 (Found: C, 81·6; H, 9·2. Calc. for $C_{13}H_{18}O$: C, 81·8; H, 9·1%). A sample prepared from mesityl oxide and phenylmagnesium bromide had b. p. 56°/2 × 10^{-4} mm., n_D^{20} 1·5287 (Ravier, *Compt. rend.*, 1934, **198**, 1786, gives b. p. 95—96°/9 mm., n_D^{20} 1·534. The high refractive index recorded by this author is probably due to some rearranged or dehydrated material). Light absorption in ethanol: Max. 2510 A., ε = 245; inflection 2580 A., ε = 235.

Hydrogenation of the carbinol (1·3 g.) in ethyl acetate (20 ml.) in the presence of platinic oxide resulted in the uptake of 1 mole of hydrogen to give phenylmethyl*iso*butylcarbinol (0·8 g.), b. p. 64°/10^{-3} mm., n_D^{18} 1·5058; Bodroux and Taboury (*Compt. rend.*, 1909, **148**, 1676; *Bull. Soc. chim.*, 1909, **5**, 813) give b. p. 125—128°/18 mm., n_D^{15} 1·5157.

α-Methylstyryldimethylcarbinol (*4-Phenyl-2-methylpent-3-en-2-ol*) (IX) *and* *4-Phenyl-2-methylpenta-1 : 3-diene* (X).—(*a*) A solution of phenylmethyl*iso*butenylcarbinol (8 g.) in 60% aqueous acetone (200 ml.) containing hydrochloric acid (0·02M.) was set aside for 3 hours at room temperature, and the solution was then made just alkaline with aqueous 2N-sodium hydroxide. Isolation of the products in the usual manner afforded *α-methylstyryldimethylcarbinol* (6·5 g.), b. p. 85—88°/10^{-3} mm., n_D^{20} 1·5430 (Found: C, 82·0, 81·6; H, 8·9, 9·2. $C_{13}H_{18}O$ requires C, 81·8; H, 9·1%). Active hydrogen, determined by the method of Braude and Stern, *J.*, 1946, 404): 1·01, 0·99. Light absorption: see Table.

Hydrogenation of the carbinol (3 g.) in methanol (30 ml.) resulted in the uptake of 1 mole of hydrogen, to give *4-phenyl-2-methylpentan-2-ol* (2·5 g.), b. p. 66—68°/10^{-3} mm., n_D^{17} 1·5061 (Found: C, 80·8; H, 10·1. $C_{12}H_{18}O$ requires C, 80·8; H, 10·2%). The 3 : 5-*dinitrobenzoate* crystallised from *n*-hexane–benzene in plates, m. p. 97—98°, undepressed on admixture with the specimen described below (*c*) (Found: C, 61·4; H, 5·6; N, 7·7. $C_{19}H_{20}O_6N_2$ requires C, 61·3; H, 5·4; N, 7·5%).

(*b*) Phenylmethyl*iso*butenylcarbinol (27 g.) was shaken with 2N-sulphuric acid (100 ml.) for 24 hours. The upper layer was separated and dried (Na_2SO_4–K_2CO_3). Fractionation from a trace of potassium carbonate afforded α-methylstyryldimethylcarbinol (12 g.), b. p. 72—75°/10^{-3} mm., n_D^{20} 1·5412, and impure 2-phenyl-4-methylpenta-2 : 4-diene, b. p. 63—66°/0·1 mm., n_D^{20} 1·5537 (Found: C, 89·9; H, 9·4. Calc. for $C_{12}H_{14}$: C, 91·1; H, 8·9%). Light absorption in ethanol: Max. 2510, 2580, 2660, and 2760 A., ε = 11,000, 12,000, 11,000, and 9,000, respectively.

(*c*) Ethyl β-methylcinnamate (9·5 g.) [prepared by the method of Lindenbaum (*Ber.*, 1917, **50**, 1270) but without isolation of the intermediate hydroxy-ester], b. p. 83—85°/0·2 mm., n_D^{20} 1·5438 (Kon and Johnson, *J.*, 1926, 2752, give b. p. 142—145°/16 mm., n_D^{15} 1·5451), was treated with methylmagnesium bromide (from Mg, 3 g.), to give α-methylstyryldimethylcarbinol (5 g.), b. p. 86—87°/0·05 mm., n_D^{20} 1·5423 (Found: C, 82·3; H, 9·2%). Light absorption: identical with that of the sample obtained under (*a*). Catalytic hydrogenation as above gave 2-methyl-4-phenylpentan-2-ol [3 : 5-dinitrobenzoate, m. p. 97—98°, undepressed on admixture with the specimen prepared as in (*a*)].

α-Methylstyrene.—Phenyldimethylcarbinol (Tissier and Grignard, *Compt. rend.*, 1901, **132**, 1184) [*p-nitrobenzoate*, m. p. 134—135° (Found: C, 67·2; H, 5·5; N, 4·8. $C_{16}H_{15}O_4N$ requires C, 67·4; H, 5·3; N, 4·9%)] was dehydrated, by distillation from potassium hydrogen sulphate (Perkin and Matsubara, *J.*, 1905, **87**, 671), to α-methylstyrene, b. p. 165°, n_D^{18} 1·5407. Light absorption: see Table. In one experiment, a *dimer* of α-methylstyrene, b. p. 147—152°/1 mm., n_D^{20} 1·5667 [Found: C, 91·6; H, 8·8%; *M* (in camphor), 232. $C_{18}H_{20}$ requires C, 91·5; H, 8·5%; *M*, 236], was obtained as sole product. Light absorption in ethanol: Max. 2420 A., ε = 13,500. An analogous dimer from *p*-methyl-α-methylstyrene is described by Hukki (*Acta Chem. Scand.*, 1949, **3**, 279).

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411. *Alkenylation by Use of Lithium Alkenyls. Part II. The Condensation of isoButenyl-lithium with Acraldehyde and Crotonaldehyde, and the Oxotropic Rearrangement of the Resulting Carbinols. (Studies in Molecular Rearrangement. Part IV.)*

By E. A. Braude and C. J. Timmons.

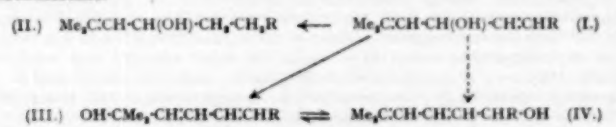
*iso*Butenyl-lithium (see Part I, preceding paper) condenses normally with acraldehyde and crotonaldehyde to give the expected substituted divinylcarbinols (I*a* and I*b*), the constitutions of which are proved by catalytic hydrogenation. The *iso*butenyl group in propenyl*iso*butenylcarbinol (I*b*) is surprisingly resistant to hydrogenation with a platinic oxide catalyst.

On treatment with very dilute mineral acids, the divinylcarbinols undergo irreversible oxotropic rearrangement to give exclusively the substituted tertiary butadienylcarbinols (III). Under more strongly acid conditions, the latter undergo further reversible rearrangement to the primary or secondary isomers (IV), as well as partial dehydration to the substituted hexatrienes (V).

In Part I (preceding paper) condensation of *iso*butenyl-lithium with benzaldehyde and acetophenone has been described. These reactions showed that the alk-1-enyl-lithium derivative behaves normally towards carbonyl compounds, but the synthesis of arylalkenylcarbinols by this route is of limited preparative value as these are also accessible through the arylmagnesium derivatives. The present work provides some examples of the use of *iso*butenyl-lithium for the synthesis of otherwise relatively inaccessible dialkenylcarbinols.

*iso*Butenyl-lithium reacted in the expected manner with acraldehyde and crotonaldehyde to give the substituted divinylcarbinols, vinyl- (I*a*) and propenyl-*iso*butenylcarbinol (I*b*) in 40% yields. Only a few simple carbinols of this type have previously been described, though some of the lower homologues, including divinylcarbinol itself, have been prepared by semi-hydrogenation of the corresponding ethynylcarbinols (Lespieau and Lombard, *Bull. Soc. chim.*, 1935, **2**, 372; Heilbron, Jones, McCombie, and Weedon, *J.*, 1945, **84**, 88). A higher homologue, methyldi-*iso*butenylcarbinol, has also been obtained by the condensation of phorone and methylmagnesium iodide (Fellenberg, *Ber.*, 1904, **37**, 3578).

The structures of (I*a*) and (I*b*) were proved by their transparency in the 2300-A. region and by catalytic hydrogenation to ethyl- and propyl-*iso*butylcarbinol, respectively. The carbinol (I*a*) readily absorbed two moles of hydrogen, when dry methanol was used as solvent and platinic oxide as catalyst. With (I*b*), the uptake of hydrogen practically ceased after one mole had been absorbed. The semi-hydrogenated product furnished acetone, but no propaldehyde on ozonisation, and is therefore propyl*iso*butenylcarbinol (II; R = Me). Further hydrogenation of the latter, over a palladium–calcium carbonate catalyst, resulted in the smooth uptake of a second mole of hydrogen to give propyl*iso*butylcarbinol. In view of the ready and complete hydrogenation of (I*a*) over platinum oxide, the resistance of the *iso*butenyl group in (I*b*) to hydrogenation in these conditions is rather surprising: the introduction of the additional methyl substituent in (I*b*) would not be expected to have any pronounced effect on the accommodation of the *iso*butenyl group on the catalyst. A somewhat similar observation has recently been reported, however, by Zafiriadis (*Compt. rend.*, 1948, **226**, 731) who found that ethyl cinnamylideneethyl ketone is considerably more resistant to catalytic hydrogenation than cinnamylideneacetone.



Propenyl*iso*butenylcarbinol also proved surprisingly resistant to oxidation by the Oppenauer method, no significant yield of the expected ketone being obtained on prolonged treatment with acetone and aluminium *tert.*-butoxide in boiling benzene. When *p*-benzoquinone, a more powerful hydrogen acceptor, is used, oxidation does occur, but the quinol produced immediately

acts as acidic catalyst causing rearrangement of the carbinol, and the product isolated is mainly 6-methylhepta-3 : 5-dien-2-one, derived from the isomeric carbinol (IV*b*) (see below).

The acid-catalysed oxotropic rearrangement of divinylcarbinols was first described by Heilbron, Jones, McCombie, and Weedon (*loc. cit.*) who showed that divinylcarbinol itself is converted into penta-2 : 4-dien-1-ol on treatment with dilute acids, and that vinylpropenylcarbinol (VII) is similarly converted into hexa-3 : 5-dien-2-ol (VIII). The rearrangement of vinylpropenylcarbinol could theoretically proceed in two directions, with migration of the hydroxyl group to either the unsubstituted or the methyl-substituted γ-carbon atom, but none of the alternative rearrangement product, sorbyl alcohol (IX), was obtained and the exclusive formation of (VIII) was ascribed to the superior electron-donating properties of the propenyl compared with the vinyl group.

$$\mathrm{CHMe{:}CH{\cdot}CH(OH){\cdot}CH{:}CH_2} \quad \text{(VII.)}$$

$$\text{(VIII.)}\ \mathrm{OH{\cdot}CHMe{\cdot}CH{:}CH{\cdot}CH{:}CH_2} \rightleftharpoons \mathrm{CHMe{:}CH{\cdot}CH{:}CH{\cdot}CH_2{\cdot}OH}\ \text{(IX.)}$$

Since the ease of rearrangement of vinylpropenylcarbinol is much greater than that of divinylcarbinol (Braude and Jones, *J.*, 1946, 128), a rapidly increasing order of mobility was to be expected for the oxotropic systems represented by (I*a*) and (I*b*). Treatment of the two carbinols with 0·001M-sulphuric acid in aqueous acetone at room temperature for 4 hours and for 10 minutes, respectively, results in quantitative isomerisation to the conjugated tertiary carbinols, dimethylbutadienylcarbinol (2-methylhexa-3 : 5-dien-2-ol) (III*a*) and dimethylpentadienylcarbinol (2-methylhepta-3 : 5-dien-2-ol) (III*b*), which exhibit ultra-violet light absorption properties typical of mono- and di-alkylated conjugated dienes (see Table) and were characterised by their maleic anhydride adducts. The adducts contain one free carboxyl group as shown by alkalimetric titration and are therefore lactonic acids analogous to those obtained from lower homologues (Heilbron *et al.*, *loc. cit.*). The lability of (I*a*) and, even more so, of (I*b*) is so great that unless careful precautions are taken to eliminate all traces of acids during their preparation, partly or largely rearranged products are obtained. The carbinol (III*a*) has previously been prepared from two different acetylenic precursors by Nazarov and Fisher (*Bull. Acad. Sci. U.R.S.S., Cl. Sci. Chim.*, 1945, 631; 1948, 311), and the physical constants obtained in the present work are in good agreement with those previously recorded. The structure of (III*b*) was proved by catalytic hydrogenation in the presence of platinic oxide to give dimethyl-*n*-amylcarbinol, identified by the 3 : 5-dinitrobenzoate.

On treatment with more concentrated mineral acids, *e.g.*, when shaken with 0·1M-aqueous hydrochloric acid, (I*a*) is converted into an approximately equimolar mixture of the tertiary isomer (III*a*) and the primary isomer, 5-methylhexa-2 : 4-dien-1-ol (IV*a*), which could be separated by fractional distillation. The primary isomer (IV*a*) can readily be distinguished from (III*a*) by its longer wave-length absorption maximum, which has the location expected for a trialkylated conjugated diene (see Table), and like 1 : 1 : 4-trimethylbutadiene (Bacon and Farmer, *J.*, 1937, 1065, erroneously quoted by Norton, *Chem. Reviews*, 1942, **31**, 369; Henne and Turk, *J. Amer. Chem. Soc.*, 1942, **64**, 826) fails to give a crystalline maleic anhydride adduct. An approximately equimolar mixture of (III*a*) and (IV*a*) is also obtained by the acid treatment of (III*a*). Quantitative kinetic measurements (which will be reported in detail in a separate communication) show that the rearrangement (III*a*) ⟶ (IV*a*) is slower by a factor of *ca.* 10^5 than the rearrangement (I*a*) ⟶ (III*a*), and that (IV*a*) is not formed *directly* from (I*a*) to any measurable extent even under the more strongly acid conditions. The rearrangement (III*a*) ⟶ (IV*a*) represents a five-carbon oxotropic change and is reversible, (IV*a*) being isomerised similarly. Isomerisation in homogeneous solution is accompanied by some dehydration of (III*a*) to 2-methylhexa-1 : 3 : 5-triene (VI*a*).

The isomerisation of (III*a*) and (IV*a*) has previously been reported by Nazarov and Fisher (*locc. cit.*) who, however, employed somewhat different conditions and were only able to effect *ca.* 20% conversion, without establishing equilibria. The same workers have also recently described (*loc. cit.*, 1948) the partial interconversion of the lower homologues, methylbutadienylcarbinol (VIII) and sorbyl alcohol (IX).

The higher homologue (III*b*) similarly undergoes further isomerisation to an approximately equimolar mixture of (III*b*) and the secondary conjugated isomer, 6-methylhepta-3 : 5-dien-2-ol (IV*b*), but in this case a complete separation of the two isomers by fractionation could not be readily effected. The isomers (III*b*) and (IV*b*) again differ in the location of their ultra-violet

absorption maxima (see Table), and (IV*b*) does not furnish a maleic anhydride adduct. As in the case of (III*a*), the further rearrangement of (III*b*) in homogeneous solution is accompanied by some dehydration; a sample of the resulting 2-methylhepta-1 : 3 : 5-triene (V*b*), which exhibited the expected light-absorption properties (see Table), was also obtained by the combined rearrangement and dehydration of (I*b*) with potassium hydrogen sulphate, but sufficient material was not available for complete purification.

The structure of (IV*b*) was proved by oxidation of the equilibrium mixture of (III*b*) and (IV*b*) with *p*-benzoquinone and aluminium *tert.*-butoxide in boiling benzene. The tertiary carbinol (III*b*) is unaffected by the Oppenauer reagent, whereas (IV*b*) is oxidised to 6-methylhepta-3 : 5-dien-2-one (VI*b*). The quinol produced in the reaction acts as acidic catalyst, converting more (III*b*) into (IV*b*) as the oxidation proceeds. The dienone has previously been obtained by Kuhn and Hoffer (*Ber.*, 1932, **65**, *B*, 651) by the condensation of acetone and β-methylcrotonaldehyde. Since the latter is not very readily accessible, the dienone was more conveniently prepared from β-methylcrotonic acid by reduction with lithium aluminium hydride to 2-methylcrotyl alcohol, followed by simultaneous oxidation and condensation with acetone in the presence of aluminium *tert.*-butoxide (cf. Heilbron *et al.* *J.*, 1938, 175; 1949, 2031). The dienone was identified as semicarbazone and 2 : 4-dinitrophenylhydrazone.

Ultra-violet light absorption properties of substituted butadienes and butadienylcarbinols in ethanol.

	$\lambda_{max.}$, Å.	$\varepsilon_{max.}$	Substitution.
$CH_2{=}CH{\cdot}CH{=}CHMe$	2235	23,000 [1]	Mono
$CH_2{=}CH{\cdot}CH{=}CH{\cdot}CH_2{\cdot}OH$	2250	25,000 [2]	,,
$CH_2{=}CH{\cdot}CH{=}CH{\cdot}CHMe{\cdot}OH$	2220	28,000 [2]	,,
$CH_2{=}CH{\cdot}CH{=}CH{\cdot}CMe_2{\cdot}OH$ (III*a*)	2235	26,000	,,
$CHMe{=}CH{\cdot}CH{=}CHMe$	2270	22,500 [1]	Di
$CHMe{=}CH{\cdot}CH{=}CH{\cdot}CMe_2{\cdot}OH$ (III*b*)	2270	26,000	,,
$Me_2C{=}CH{\cdot}CH{=}CH{\cdot}CH_2{\cdot}OH$ (IV*a*)	2360	18,700	Tri
$Me_2C{=}CH{\cdot}CH{=}CH{\cdot}CHMe{\cdot}OH$ (IV*b*)	2360	22,300	,,

[1] Booker, Evans, and Gillam, *J.*, 1940, 1453.
[2] Heilbron, Jones, McCombie, and Weedon, *J.*, 1945, 84.

The work described above shows that unsymmetrically substituted divinylcarbinols initially undergo irreversible rearrangement, the hydroxyl group migrating exclusively to the more highly substituted γ-carbon atom, and that the resulting butadienylcarbinols then undergo a further, much slower, reversible rearrangement to the primary or secondary isomers. The fact that the equilibrium mixtures formed in the latter rearrangements contain approximately equal proportions of the tertiary and primary or secondary isomers shows that, although the mobility of the five-carbon oxotropy is much smaller than that of the preceding three-carbon oxotropy, the stabilities of the two possible final products are very similar. It might, therefore, at first sight, appear somewhat surprising that the initial rearrangement should proceed exclusively in one direction. Our interpretation of these phenomena is, briefly, as follows (a more detailed discussion will be presented later in conjunction with kinetic data). The direction of the initial rearrangement will be determined by the relative ease of electron-withdrawal from the two γ-carbon atoms, because the rate-determining step involves the detachment of a water molecule at the α-carbon atom and the simultaneous migration of the double-bond electron pair from the βγ- to the αβ-position (Braude and Jones, *loc. cit.*; Braude, *J.*, 1948, 794). Methyl substituents facilitate electron-withdrawal from the carbon atom to which they are attached, and will therefore influence the relative rates of two possible rearrangements of the same carbinol in the same way as they influence the relative rates of the same rearrangement in two different carbinols. A γ-methyl substituent generally increases the rate of rearrangement by a factor of over 100; hence (III) might be expected to be formed from (I) at least 100 times faster than (IV), and, under conditions which cause the rearrangement into (III) to proceed at a measurable rate, the amount of (IV) formed will be undetectably small. The position of the equilibrium in the subsequent five-carbon oxotropy will similarly be governed by the relative rates of the opposing reactions, (III) ⟶ (IV), and (IV) ⟶ (III). Now, (III) and (IV) differ only in the disposition of methyl substituents on the α- and ε-carbon atoms. Quantitative data on the relative effects of α- and ε-methyl substituents are not at present available, but they may be expected to be of the same order. Therefore, the forward and backward rates of the reaction (III) ⇌ (IV) will be similar, and the equilibrium will be evenly balanced. Analogous considerations will, of course, apply to the rearrangements of the lower homologue (VII) ⟶ (VIII) ⇌ (IX).

The equilibria can also be discussed from a slightly different point of view, in terms of energetic considerations (cf. Braude and Stern, *J.*, 1947, 1096; Catchpole, Hughes, and Ingold, *J.*, 1948, 16). The difference in energy levels of the unconjugated and conjugated isomers will be comparatively large (*ca.* 7 kcals./g.-mol.), corresponding to the resonance energy of the butadiene system formed in the three-carbon oxotropic rearrangement, which is therefore, for practical purposes irreversible. The difference in energy levels of the two conjugated isomers, on the other hand, will be comparatively small, corresponding only to the change in hyperconjugation energy (*ca.* 2 kcals./g.-mol.) arising from the different number of alkyl substituents directly attached to the conjugated system, and the five-carbon rearrangement is, therefore, reversible.

Experimental.

(M. p.s were determined on a Kofler block and are corrected.)

Vinylisobutenylcarbinol (*5-Methylhexa-1 : 4-dien-3-ol*) (Ia).—Acraldehyde (25 g.) in ether (75 ml.) was added dropwise to a stirred, ethereal solution of *iso*butenyl-lithium (from Li, 7 g.) at 10° (see Part I, preceding paper). After a further ½ hour's stirring at room temperature, saturated ammonium chloride solution (200 ml.) was added, and the ethereal layer was separated and dried (Na_2SO_4–K_2CO_3). The ether was removed by distillation through a column, and the residue fractionated from a trace of potassium carbonate to give *vinylisobutenylcarbinol* (18 g., 36%) as a colourless liquid, b. p. 57°/8 mm., n_D^{15} 1·4614 (Found : C, 74·9; H, 10·9. $C_7H_{12}O$ requires C, 75·0; H, 10·8%). Light absorption in ethanol : $\varepsilon < 500$ in the range 2200—4000 A.

Hydrogenation of the carbinol (1·6 g.) in methanol (20 ml.) in the presence of platinic oxide and a little potassium carbonate resulted in the uptake of 2 moles of hydrogen to give ethyl*iso*butylcarbinol (1·2 g.), b. p. 100—102°/140 mm., n_D^{15} 1·4170, which was oxidised with potassium dichromate in sulphuric acid to ethyl *iso*butyl ketone, identified by the semicarbazone, m. p. 149—153° (Nazarov, *Bull. Acad. Sci. U.R.S.S.*, 1940, 545, gives m. p. 148—149°), and by the 2 : 4-dinitrophenylhydrazone, m. p. 74—76° (Allen, *J. Amer. Chem. Soc.*, 1930, **52**, 2955, gives m. p. 75°), both undepressed on admixture with authentic samples.

Dimethylbutadienylcarbinol (*2-Methylhexa-3 : 5-dien-2-ol*) (IIIa).—A solution of vinyl*iso*butenylcarbinol (9 g.) in 60% aqueous acetone (200 ml.) containing sulphuric acid (0·001M.) was set aside for 4 hours at room temperature. The solution was made just alkaline with aqueous 2N-sodium hydroxide and most of the acetone was distilled off through a column. The residue was diluted with water (50 ml.) and extracted with ether. Fractionation of the ethereal extract afforded 2-methylhexa-3 : 5-dien-2-ol (7 g.), b. p. 92—93°/85 mm., n_D^{20} 1·4758 (Found : C, 74·9; H, 11·0. Calc. for $C_7H_{12}O$: C, 75·0; H, 10·8%) (Nazarov and Fisher, *Bull. Acad. Sci. U.R.S.S., Cl. sci. chim.*, 1945, 631; 1948, 311, give b. p. 44—45°/10 mm., n_D^{20} 1·4710, 1·4760). Light absorption in ethanol : see Table.

A solution of the carbinol (1 g.) and maleic anhydride (1 g.) in benzene (10 ml.) was set aside for 3 days at room temperature. The lactonic *acid* (0·7 g.) which separated crystallised from water in needles and sublimed in plates, m. p. 204—207° (Found : C, 62·8; H, 6·8; equiv. by titration with 0·01M-KOH, 212. $C_{12}H_{16}O_5{\cdot}CO_2H$ requires C, 62·9; H, 6·7%; equiv., 210).

5-Methylhexa-2 : 4-dien-1-ol (IVa) *and 2-Methylhexa-1 : 3 : 5-triene* (Va).—(*a*) Vinyl*iso*butenylcarbinol (12 g.) was shaken for 17 hours with aqueous 0·1M-hydrochloric acid (15 ml.). The upper layer was separated and dried (Na_2SO_4–K_2CO_3). Fractionation from a trace of potassium carbonate afforded 2-methylhexa-3 : 5-dien-2-ol (5 g.), b. p. 56°/12 mm., n_D^{15} 1·4763, $\lambda_{max.}$ 2235 A., ε = 26,000, and 5-methylhexa-2 : 4-dien-1-ol (3 g.), b. p. 87°/12 mm., n_D^{15} 1·4996 (Found : C, 74·5; H, 10·8. Calc. for $C_7H_{12}O$: C, 75·0; H, 10·8%) (Nazarov and Fisher, *loc. cit.*, give b. p. 76—78°/8 mm., n_D^{20} 1·5060). Light absorption in ethanol : see Table.

(*b*) A solution of 2-methylhexa-3 : 5-dien-2-ol (6 g.) in 80% aqueous acetone (100 ml.) containing sulphuric acid (0·04M.) was allowed to stand for 5 days at room temperature. Isolation of the products as before afforded 2-methylhexa-3 : 5-dien-2-ol (2 g.), 5-methylhexa-2 : 4-dien-1-ol (2 g.), and impure 2-methylhexa-1 : 3 : 5-triene (1 g.), b. p. 48—52°/110 mm., n_D^{15} 1·5127. The triene, which rapidly polymerised, was also obtained by distilling 2-methylhexa-3 : 5-dien-2-ol from potassium hydrogen sulphate, and had light absorption in ethanol : Max. 2480, 2570, and 2670 A., ε = 21,000, 28,000, and 22,000, respectively.

Propenylisobutenylcarbinol (*2-Methylhepta-2 : 5-dien-4-ol*) (Ib).—Crotonaldehyde (30 g.) in ether (60 ml.) was added drop-wise to a stirred, ethereal solution of *iso*butenyl-lithium (from Li, 7 g.) at 10°. Stirring was continued at room temperature for 2 hours, and saturated aqueous ammonium chloride solution (200 ml.) was added. Isolation of the products in the usual manner afforded *propenylisobutenylcarbinol* (26 g., 40%), b. p. 74°/6 mm., n_D^{15} 1·4686 (Found : C, 76·2; H, 11·1. $C_8H_{14}O$ requires C, 76·1; H, 11·2%). Light absorption in ethanol $\varepsilon < 1000$ in the range 2200—4000 A. Attempted oxidation of the carbinol by heating it with acetone and aluminium *tert.*-butoxide in benzene for 24 hours under reflux gave no significant amount of high-boiling ketonic material. Oxidation with *p*-benzoquinone is accompanied by rearrangement, giving 2-methylhepta-2 : 4-dien-6-one (see below).

Propylisobutenylcarbinol (*2-Methylhept-2-en-4-ol*) (IIb) *and Propylisobutylcarbinol* (*2-Methylheptan-4-ol*).—Hydrogenation of propenyl*iso*butenylcarbinol (9 g.) in methanol (50 ml.) in the presence of platinic oxide and a trace of potassium carbonate resulted in the uptake of 1 mole of hydrogen (1760 ml. at 18°/768 mm.), to give *propylisobutenylcarbinol* (8·5 g.), b. p. 73—75°/12 mm., n_D^{15} 1·4444 (Found : C, 75·0; H, 12·8. $C_8H_{16}O$ requires C, 74·9; H, 12·7%). The 3 : 5-*dinitrobenzoate* separated from pentane in colourless needles, m. p. 46—48° (Found : N, 9·0. $C_{15}H_{18}O_6N_2$ requires N, 9·0%). Ozonisation of

the carbinol (1·8 g.) in acetic acid solution afforded acetone, isolated as the 2 : 4-dinitrophenylhydrazone (1·9 g.), m. p. 127—128°, undepressed on admixture with an authentic specimen but depressed to 105—112° on admixture with the propaldehyde derivative.

Hydrogenation of propyl*iso*butenylcarbinol (1·8 g.) in methanol (30 ml.) in the presence of a 5% palladium–calcium carbonate catalyst (0·5 g.) resulted in the uptake of 1 mole of hydrogen to give propyl*iso*butylcarbinol (1 g.), b. p. 113—114°/130 mm., n_D^{20} 1·4198. An authentic specimen of the latter was prepared from *iso*valeraldehyde and *n*-propylmagnesium bromide (Muset, *Chem. Zentr.*, 1907, I, 1313, gives b. p. 160°, n_D 1·4203). Both samples gave the same **3** : 5-*dinitrobenzoate*, which crystallised from pentane in plates, m. p. 66—68° (Found : C, 54·2; H, 6·4; N, 9·0. $C_{14}H_{18}O_6N_2$ requires C, 53·8; H, 6·4; N, 9·0%).

Dimethylpentadienylcarbinol (2-*Methylhepta*-**3** : 5-*dien*-2-*ol*) (III*b*).—A solution of propenyl*iso*butenylcarbinol (9 g.) in 80% aqueous acetone (200 ml.) containing sulphuric acid (0·001M.) was kept at room temperature for 10 minutes. Isolation of the product in the usual manner afforded 2-*methylhepta*-**3** : 5-*dien*-2-*ol* (7 g.), b. p. 68—69°/9 mm., n_D^{20} 1·4850 (Found : C, 76·1; H, 10·8. $C_8H_{14}O$ requires C, 76·1; H, 11·2%). Light absorption in ethanol : see Table. The isomerisation could also be effected with a variety of other weakly acidic reagents, *e.g.*, dilute solutions of acetic acid, potassium dihydrogen phosphate, or quinol. No rearrangement, on the other hand, was observed on treatment with M-potassium *tert.*-butoxide in *tert.*-butanol for 24 hours at 78°.

A solution of the carbinol (1 g.) and maleic anhydride (1 g.) in benzene (3 ml.) was kept at room temperature for 6 days. The lactonic *acid* (0·7 g.) which separated crystallised from aqueous methanol as needles, m. p. 204—206° (Found : C, 64·8; H, 7·4%; equiv. by titration with 0·01M-KOH, 226. $C_{12}H_{14}O_4$ requires C, 64·3; H, 7·2%; equiv., 224).

Hydrogenation of the carbinol (2 g.) in methanol in the presence of platinic oxide resulted in the uptake of 2 moles of hydrogen to give dimethyl-*n*-amylcarbinol (1·5 g.), b. p. 74°/18 mm., n_D^{15} 1·4248. An authentic specimen of the latter, prepared from *n*-amylmagnesium bromide and acetone, had b. p. 106°/109 mm., n_D^{15} 1·4199 (Muset, *loc. cit.*, gives b. p. 162°/760 mm., n_D 1·4303). Both samples with **3** : 5-dinitrobenzoyl chloride in pyridine gave the same **3** : 5-*dinitrobenzoate*, which crystallised from pentane in needles, m. p. 47—48° (Found : C, 54·2; H, 6·5; N, 8·8. $C_{14}H_{18}O_6N_2$ requires C, 53·8; H, 6·5; N, 9·0%). Light absorption in ethanol : Max. 2260 A., ε = 27,000. The **3** : 5-dinitrobenzoate was also prepared by treating the carbinol in pyridine with **3** : 5-*dinitrobenzoyl bromide*. This bromide was obtained on treating the acid with phosphorus pentabromide and extracting the crude product with pentane in a Soxhlet apparatus. It crystallised from pentane in needles, m. p. 61—62° (Found : C, 31·2; H, 1·0; N, 10·4; Br, 29·1. $C_{11}H_9O_5N_2Br$ requires C, 30·6; H, 1·10; N, 10·2; Br, 29·0%).

6-*Methylhepta*-**3** : 5-*dien*-2-*ol* (IV*b*) *and* 2-*Methylhepta*-**1** : **3** : 5-*triene* (V*b*).—(*a*) Propenyl*iso*butenylcarbinol (10 g.) was shaken with aqueous 0·01M-hydrochloric acid for 12 hours at room temperature. Isolation of the products in the usual manner afforded a mixture (9 g.) of 2-methylhepta-**3** : 5-dien-2-ol and 6-methylhepta-**3** : 5-dien-2-ol. Ultra-violet light absorption data showed that the two isomers were present in approximately equal proportions ($\lambda_{max.}$ 2300 and 2360 A., ε = 22,500 and 22,500 respectively). Only partial separation was achieved on fractionation, the fraction containing the highest proportion of the secondary carbinol having b. p. 78—80°/9 mm., n_D^{15} 1·4975 (Found : C, 75·6; H, 10·6. Calc. for $C_8H_{14}O$: C, 76·1; H, 11·2%).

(*b*) A solution of 2-methylhepta-**3** : 5-dien-2-ol (6 g.) in 80% aqueous acetone (100 ml.) containing sulphuric acid (0·001M.), kept at room temperature for 2 days, afforded a mixture (4 g.) of the carbinol and its secondary isomer in about equal proportions, and impure 2-methylhepta-**1** : **3** : 5-triene (1 g.), b. p. 66—68°/100 mm., n_D^{15} 1·5246 (Found : C, 85·9, H, 11·6. Calc. for C_8H_{12} : C, 88·9; H, 11·2%). The triene was also obtained on distilling propenyl*iso*butenylcarbinol from potassium hydrogen sulphate. Light absorption in ethanol : Max. 2610 and 1710 A., ε = 41,000 and 31,000, respectively; inflection 2510 A., ε = 29,000.

6-*Methylhepta*-**3** : 5-*dien*-2-*one* (VI*b*).—(*a*) Propenyl*iso*butenylcarbinol, or an equilibrium mixture of 2-methyl- and 6-methyl-hepta-**3** : 5-dien-2-ol (see above) (5·0 g.), aluminium *tert.*-butoxide (10 g.), *p*-benzoquinone (5 g.), and benzene (50 ml.) were heated for 5 hours under reflux. The mixture was acidified with dilute sulphuric acid and extracted with ether. Fractionation of the ethereal extract afforded 6-methylhepta-**3** : 5-dien-2-one, b. p. 83°/16 mm. (2 : 4-dinitrophenylhydrazone, m. p. 219—221°, undepressed on admixture with the authentic specimen described below).

(*b*) β-Methylcrotonic acid (5·5 g.) was reduced by treatment with lithium aluminium hydride (3·0 g.) in boiling ether (Nystrom and Brown, *J. Amer. Chem. Soc.*, 1947, **69**, 2548) to 2-methylcrotyl alcohol (3·8 g.), b. p. 84—86°/80 mm., n_D^{20} 1·4382 (Lennartz, *Ber.*, 1943, **76**, *B*, 841, gives b. p. 48°/11 mm., n_D^{17} 1·4420). The alcohol was heated with acetone (20 ml.), aluminium *tert.*-butoxide (8 g.), and benzene (50 ml.) for 30 hours under reflux, to give the dienone, b. p. 45°/0·3 mm., n_D^{20} 1·5278 (Kuhn and Hoffer, *Ber.*, 1932, **65**, *B*, 651, give b. p. 86—87°/15 mm., n_D^{15} 1·5292). Light absorption in ethanol : Max. 2860 A., ε = 18,000. The semicarbazone had m. p. 189—192° (Fischer and Löwenberg, *Annalen*, 1932, **494**, 263, give m. p. 192°). The 2 : 4-*dinitrophenylhydrazone* crystallised from benzene in bright red needles, m. p. 217—220° (Found : C, 55·6; H, 5·6; N, 18·6. $C_{14}H_{16}O_4N_4$ requires C, 55·3; H, 5·3; N, 18·4%). Light absorption in chloroform : Max. 2700, 3080, and 3990 A., ε = 20,000, 21,600, and 38,000 respectively; inflection 2800 A., ε = 13,500.

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412. *Alkenylation by Use of Lithium Alkenyls. Part III. The Synthesis of Unsaturated Ketones from* iso*Butenyl-lithium.*

By E. A. Braude and J. A. Coles.

*iso*Butenyl-lithium (cf. Part I, *J.*, 1950, 2000) reacts with lithium acetate, benzoate, or crotonate to give mesityl oxide, phenyl *iso*butenyl ketone, or propenyl *iso*butenyl ketone, respectively. Only poor yields of ketones are obtained from the reaction between *iso*butenyl-lithium and the acid chlorides.

Propenyl *iso*butenyl ketone, the structure of which is proved by catalytic hydrogenation, undergoes 1 : 4-addition with methylmagnesium bromide to give *iso*butyl *iso*butenyl ketone.

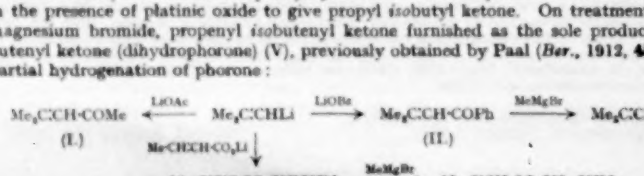
In the two preceding papers, the synthesis of unsaturated carbinols from *iso*butenyl-lithium has been described. The present work deals with the synthesis of unsaturated ketones and provides a further illustration of the usefulness of this new type of organo-metallic reagent.

A variety of carboxylic acid derivatives, including acid chlorides (Kloppenburg and Wibaut, *Rec. Trav. chim.*, 1946, **65**, 393), anhydrides (Wibaut, Kloppenburg, and Beets, *ibid.*, 1944, **63**, 134), nitriles (Ziegler *et al.*, *Annalen*, 1932, **495**, 84; 1933, **504**, 94; 1934, **512**, 164; Gilman and Kirby, *J. Amer. Chem. Soc.*, 1933, **55**, 1265), and lithium salts (Gilman and van Ess, *ibid.*, p. 1258; Arens and van Dorp, *Rec. Trav. chim.*, 1946, **65**, 338; Heilbron, Jones, and Richardson, *J.*, 1949, 287), has been employed for the synthesis of ketones from alkyl- and aryl-lithium derivatives. The last-named method appeared particularly suitable in the present case in view of the observation (Part I, *J.*, 1950, 2000) that carboxylation of *iso*butenyl-lithium affords, besides β-methylcrotonic acid, considerable proportions of phorone which must be formed by the reaction of the alkenyl-lithium with the lithium salt of the acid. An additional advantage of the use of lithium salts as secondary components is that the lithium alkenyl can be formed in their presence, thus reducing the incidence of side-reactions.

In this manner, *iso*butenyl-lithium has been condensed with lithium acetate, benzoate, or crotonate in ether to give mesityl oxide (I), phenyl *iso*butenyl ketone (II), or propenyl *iso*butenyl ketone (III). As previously (Parts I and II), appreciable amounts of the Wurtz product, 2 : 5-dimethylhexa-2 : 4-diene, are also formed, and this limits the yields of ketones to 30—40%, based on the bromide. Only small yields of ketones were obtained on treating *iso*butenyl-lithium with acetyl or crotonyl chloride, and no significant amount of ketone could be isolated after reaction with acetonitrile.

Phenyl *iso*butenyl ketone has previously been prepared by various methods (Kohler, *Amer. Chem. J.*, 1909, **42**, 398; Blaise and Herman, *Ann. Chim.*, 1911, **23**, 530; Darzens, *Compt. rend.*, 1929, **189**, 767), but the physical constants recorded for this compound are somewhat conflicting. It has now been characterised as *p*-nitrophenylhydrazone, m. p. 168°, and 2 : 4-dinitrophenylhydrazone, and was readily hydrogenated over platinum oxide to phenyl *iso*butyl ketone. The low boiling point, and the low-melting *p*-nitrophenylhydrazone (m. p. 132°) recorded by Blaise and Herman (*loc. cit.*), suggest that their product was not phenyl *iso*butenyl ketone. On treatment with methylmagnesium bromide, the ketone underwent exclusively 1 : 2-addition to give phenylmethyl*iso*butenylcarbinol (IV) (Ravier, *Compt. rend.*, 1934, **198**, 1786; Part I, *loc. cit.*). This is in contrast to the reaction with phenylmagnesium bromide which results mainly in 1 : 4-addition (Kohler, *loc. cit.*). A different behaviour of methyl- compared with ethyl- or phenyl-magnesium halide towards αβ-unsaturated carbonyl compounds has also been observed in other cases (Klages, *Ber.*, 1906, **39**, 2592; Kohler, *Amer. Chem. J.*, 1907, **38**, 529).

Apart from phorone, only few simple dialkenyl ketones have been described in the literature (Nazarov *et al.*, *Bull. Acad. Sci., U.S.S.R., Cl. Sci. Chim.*, 1945, 505; 1946, 91, 201; 1947, 641, 647; 1948, 118, 236). Propenyl *iso*butenyl ketone (III), like its lower homologues, is a pale yellow liquid and does not form a semicarbazone under the usual conditions. It was characterised by the 2 : 4-dinitrophenylhydrazone. It readily absorbed two moles of hydrogen in the presence of platinic oxide to give propyl *iso*butyl ketone. On treatment with methylmagnesium bromide, propenyl *iso*butenyl ketone furnished as the sole product *iso*butyl *iso*butenyl ketone (dihydrophorone) (V), previously obtained by Paal (*Ber.*, 1912, **45**, 2226) by the partial hydrogenation of phorone:



It was identified by the semicarbazone, m. p. 137°, and was also characterised by the 2 : 4-dinitrophenylhydrazone. The exclusive occurrence of 1 : 4-addition to the propenyl keto-group in this case is by no means unexpected, since ethylideneacetone and other propenyl ketones undergo mainly 1 : 4-addition (Kohler, *Amer. Chem. J.*, 1907, **38**, 511), whereas only 1 : 2-addition takes place with mesityl oxide, phorone (Fellenberg, *Ber.*, 1904, **37**, 3578), and phenyl *iso*butenyl ketone (see above).

Attempts to prepare vinyl *iso*butenyl ketone by the condensation of *iso*butenyl-lithium with lithium acrylate or acrylonitrile failed owing to extensive polymerisation of the acrylic derivatives under the influence of the organo-metallic reagent (cf. Beaman, *J. Amer. Chem. Soc.*, 1948, **70**, 3115). *iso*Butenyl-lithium failed to react with lithium formate or ethyl orthoformate under the usual conditions.

Experimental.

(M. p.s were determined on a Kofler block and are corrected.)

*iso*Butenyl-lithium.—As the preparation of *iso*butenyl bromide from *tert.*-butanol (Braude and Timmons, *J.*, 1950, 2000) is rather tedious, an alternative route, adapted from Farrell and Bachman (*J. Amer. Chem. Soc.*, 1935, **57**, 1281), was employed. Mesityl oxide in 400-g. batches was converted into β-methylcrotonic acid (180 g.) by treatment with specially stabilised, 15% aqueous sodium hypochlorite solution (7 l.), kindly furnished by Milton Antiseptic Limited through the courtesy of Mr. P. A. Lincoln (Barbier and Leser, *Bull. Soc. chim.*, 1905, **33**, 815). The acid (300 g.) was treated with bromine (600 g.) in carbon disulphide (1·2 l.) at 0° and the crude dibromo*iso*valeric acid (m. p. 107°; 800 g.) was refluxed with sodium carbonate (660 g.) and water (2·5 l.) for 30 minutes. Steam-distillation yielded crude *iso*butenyl bromide which was dried ($CaCl_2$) and fractionated from a small piece of sodium. The pure bromide (130 g.) had b. p. 91—92°/760 mm., n_D^{25} 1·4610 (Farrell and Bachman, *loc. cit.*, give b. p. 90—91°, n_D^{25} 1·4625; Braude and Timmons, *loc. cit.*, give b. p. 91·0—91·3°, n_D^{25} 1·4603) and reacted with finely cut lithium in sodium-dried ether after an induction period of 30 minutes. All condensations were carried out under nitrogen using the apparatus previously described.

Mesityl Oxide (I).—(a) *From lithium acetate.* To a suspension of anhydrous lithium acetate (33 g., 0·5 mol.) and lithium (6·9 g., 1 mol.) in ether (1 l.), a solution of *iso*butenyl bromide (68 g., 0·5 mol.) was added during 30 minutes. After 24 hours' stirring, the reaction mixture was cooled in a solid carbon dioxide–methanol bath and treated with excess of saturated aqueous ammonium chloride solution (500 ml.). Isolation of the products in the usual way afforded mesityl oxide (18 g., 36%) (identified by the 2 : 4-dinitrophenylhydrazone, m. p. 203°, undepressed on admixture with an authentic specimen) and 2 : 5-dimethylhexa-2 : 4-diene (7 g., 26%) (identified by the dihydrobromide, m. p. 66°; Braude and Timmons, *loc. cit.*, give m. p. 68°).

(b) *From acetyl chloride.* A solution of *iso*butenyl-lithium (from Li, 8·3 g.) in ether (1·5 l.) was filtered through glass wool under nitrogen pressure, and then added rapidly to a solution of acetyl chloride (43 ml.) in ether (50 ml.) at 0°. After 2 hours' stirring and working up in the usual way, mesityl oxide (11 g., 19%) and 2 : 5-dimethylhexa-2 : 4-diene (8 g., 30%) were obtained. No ketone was isolated from an experiment in which acetyl chloride was added directly to the *iso*butenyl-lithium solution at 0°.

(c) *From methyl cyanide.* No significant amount of mesityl oxide was obtained from the reaction between methyl cyanide (0·25 mol.) and *iso*butenyl-lithium (0·25 mol.), the main product consisting of high-boiling nitrogen-containing materials.

Phenyl iso*Butenyl Ketone* (II).—Anhydrous lithium benzoate (65 g.) was treated with *iso*butenyl-lithium (from Li, 6·9 g.) as above to give phenyl *iso*butenyl ketone (32 g., 40%), a pale yellow liquid, b. p. 120—121°/4 mm., n_D^{25} 1·5598 (Found : C, 82·1; H, 7·6. $C_{11}H_{12}O$ requires C, 82·5; H, 7·6%) (Kohler, *Amer. Chem. J.*, 1909, **42**, 398, gives b. p. 148°/22 mm.; Blaise and Herman, *Ann. Chim.*, 1911, **23**, 530, give b. p. 117°/10 mm., Darzens, *Compt. rend.*, 1929, **189**, 767, gives b. p. 134°/12 mm.) Light absorption in ethanol : Max. 2590 and 3410 A., ε = 19,600 and 140. The *p*-nitrophenylhydrazone crystallised from methanol in orange crystals, m. p. 168°, unchanged after chromatography on alumina using benzene–chloroform and after fusion (Found : C, 68·9; H, 6·2; N, 14·2. Calc. for $C_{17}H_{17}O_2N_3$: C, 69·1; H, 5·8; N, 14·2%) (Blaise and Herman, *loc. cit.*, give m. p. 132°). Light absorption in chloroform : Max. 3080 and 4250 A., ε = 5,300 and 35,400. The 2 : 4-*dinitrophenylhydrazone* crystallised from ethanol in deep-red plates, m. p. 185—186° (Found : C, 59·9; H, 4·9; N, 16·7. $C_{17}H_{16}O_5N_4$ requires C, 60·0; H, 4·7; N, 16·5%). Light absorption in chloroform : Max. 3910 A., ε = 29,000; inflections 2560 and 2780 A., ε = 17,700 and 11,600. No semicarbazone could be obtained under the usual conditions. Hydrogenation of the ketone (3 g.) in ethyl acetate (50 ml.) in the presence of platinic oxide resulted in the uptake of 420 ml. of hydrogen at 20°/760 mm. (Calc., 420 ml.) and gave phenyl *iso*butyl ketone (2·5 g.), b. p. 108°/16 mm., n_D^{25} 1·5108 (Schroeter, *Ber.*, 1907, **40**, 1601, gives b. p. 128°/25 mm., n_D^{20} 1·5139), which was characterised by the oxime, m. p. 76—77° (Rheinboldt and Roleff, *Ber.*, 1924, **57**, 1923, give m. p. 74°), semicarbazone, m. p. 209—210° (Tiffeneau and Levy, *Compt. rend.*, 1926, **183**, 970, give 210°), and 2 : 4-*dinitrophenylhydrazone*, m. p. 136° (Found : C, 59·3; H, 5·3; N, 16·0. $C_{17}H_{18}O_4N_4$ requires C, 59·7; H, 5·3; N, 16·4%). Light absorption of the last in chloroform : Max. 3660 A., ε = 25,700.

Phenylmethylisobutenylcarbinol (2-*Phenyl*-4-*methylpent*-3-*en*-2-*ol*) (IV).—Phenyl *iso*butenyl ketone (13 g.) in ether (20 ml.) was added to methylmagnesium bromide (from Mg, 2·3 g.) in ether (250 ml.) at 0°. After 2·5 hours, the complex was decomposed with saturated ammonium chloride solution (150 ml.) to give the carbinol (13 g., 91%), b. p. 66°/10^{-4} mm., n_D^{20} 1·5289, ε < 2000 at 2580 A. (Ravier, *Compt.*

rend., 1934, **198**, 1756, gives b. p. 95°/9 mm., n_D^{20} 1·534; Braude and Timmons, *loc. cit.*, give b. p. 64°/10^{-4} mm., n_D^{17} 1·5283).

Propenyl iso*Butenyl Ketone* (III).—(a) *From lithium crotonate.* Condensation of anhydrous lithium crotonate (45 g., 0·5 mol.) with *iso*butenyl-lithium as above and fractionation of the products yielded *propenyl isobutenyl ketone* (17 g., 30%), a pale yellow liquid, b. p. 72°/16 mm., n_D^{17} 1·4922 (Found : C, 76·9; H, 9·9. $C_8H_{14}O$ requires C, 77·4; H, 9·8%). Light absorption in ethanol : Max. 2560 and 3450 A., ε = 16,500 and 870. The 2 : 4-*dinitrophenylhydrazone* crystallised from methanol in deep-red plates, m. p. 141° (Found : C, 55·4; H, 5·4; N, 18·4. $C_{14}H_{18}O_4N_4$ requires C, 55·3; H, 5·3; N, 18·4%). Light absorption in chloroform : Max. 2590 and 3870 A., ε = 18,600 and 34,200. No semicarbazone could be obtained under the usual conditions. Hydrogenation of the ketone (3 g.) in ethyl acetate (50 ml.) in the presence of platinic oxide resulted in the uptake of 1100 ml. of hydrogen at 17°/766 mm. (Calc., 1150 ml.) and gave propyl *iso*butyl ketone (2·5 g.), b. p. 154°/760 mm., n_D^{20} 1·4098 (semicarbazone, m. p. 124—125°).

(b) *From crotonyl chloride.* Addition of a solution of *iso*butenyl-lithium to an ethereal solution of the chloride (48 ml.), and isolation of the products as above, afforded the ketone (6 g., 5%) (2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 141°).

iso*Butyl* iso*Butenyl Ketone* (V).—Propenyl *iso*butenyl ketone (7 g.) in ether (10 ml.) was treated with methylmagnesium bromide (from Mg, 1·4 g.) in ether (150 ml.). When worked up in the usual way, *isobutyl isobutenyl ketone* (4·5 g., 66%) was obtained as a colourless liquid, b. p. 31°/0·1 mm., n_D^{17} 1·4534 (Found : C, 77·1; H, 11·9. $C_8H_{14}O$ requires C, 77·1; H, 11·5%). Light absorption in ethanol : Max. 2390 and 3230 A., ε = 11,200 and 530, respectively. The 2 : 4-*dinitrophenylhydrazone* was chromatographed on alumina from benzene solution and crystallised from methanol in red plates, m. p. 92° (Found : N, 17·9. $C_{14}H_{20}O_4N_4$ requires N, 17·5%). Light absorption in chloroform : Max. 3720 A., ε = 28,500. No trace of a second 2 : 4-dinitrophenylhydrazone was obtained. The semicarbazone separated from light petroleum (b. p. 100—120°), having m. p. 137—138° (Paal, *Ber.*, 1912, **45**, 2226, gives m. p. 133—134°).

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413. *Alkenylation by Use of Lithium Alkenyls. Part IV. The Condensation of* cyclo*Hexenyl-lithium with Aldehydes and Ketones, and Some Reactions of the Resulting Carbinols. (Studies in Molecular Rearrangement. Part V.)*

By E. A. Braude and J. A. Coles.

1-Chloro*cyclo*hexene, when highly purified, reacts readily with lithium in ether to give *cyclo*hexenyl-lithium (I), carboxylation of which affords *cyclo*hexene-1-carboxylic acid (II) and di*cyclo*hex-1-enyl ketone (III). Condensation of *cyclo*hexenyl-lithium with benzaldehyde, benzophenone, acraldehyde, or crotonaldehyde furnishes the expected carbinols, the constitution of which is proved by catalytic hydrogenation, in 40—60% yields.

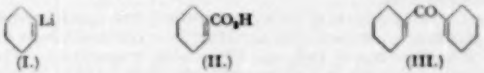
On treatment with dilute acids, *cyclo*hexenylphenyl- and *cyclo*hexenyldiphenyl-carbinol (IV) undergo oxotropic rearrangement to the *cyclo*hexylidene derivatives (V). The latter are dehydrated to the corresponding semicyclic dienes (VI), which are dehydrogenated to diphenyl- and triphenyl-methane, respectively. *cyclo*Hexenylvinylcarbinol (VIII; R = H) similarly undergoes rearrangement to the *cyclo*hexylidene derivative (IX; R = H), the constitution of which is proved by conversion into 2-*n*-propyl*cyclo*hexanone. *cyclo*Hexenylpropenylcarbinol (VIII; R = Me), unlike its lower homologue, undergoes rearrangement with migration of the hydroxyl group into the side chain, to give the isomeric carbinol (X; R = Me) which is converted by Oppenauer oxidation into the ketone (XI), a known lower homologue of β-ionone.

This paper describes, in part, the preparation and some reactions of *cyclo*hexenyl-lithium. The scope of synthetic applications of lithium alkenyls is thus extended to cyclic derivatives.

Preparation and Carboxylation of cyclo*Hexenyl-lithium.*—In the preparation of acyclic lithium alkenyls (Parts I—III, preceding papers), the easily accessible alkenyl bromides can be employed. In the *iso*cyclic series, the chlorides are much more readily prepared and fortunately proved very suitable for the purpose in hand. 1-Chloro*cyclo*hexene, when highly purified by fractionation, reacts smoothly with metallic lithium in ether, and the good yields of condensation products obtained with carbonyl compounds (see below) show that the chloride is converted into *cyclo*hexenyl-lithium to the extent of 60% or more. In contrast to the behaviour of *iso*butenyl bromide (Part I), metalation of *cyclo*hexenyl chloride with lithium is not

accompanied by a coupling reaction, and no di*cyclo*hexenyl is formed. *cyclo*Hexenyl chloride did not react appreciably with magnesium, or with sodium in ether, even in the presence of benzophenone, which was recovered unchanged.

An ethereal solution of *cyclo*hexenyl-lithium with excess of solid carbon dioxide afforded a mixture of the expected carboxylic acid, *cyclo*hexene-1-carboxylic acid (II), and the expected ketone, di(*cyclo*hex-1-enyl) ketone (III). The acid was identified by its melting point and as the amide. The ketone was characterised by the 2 : 4-dinitrophenylhydrazone, but, like other

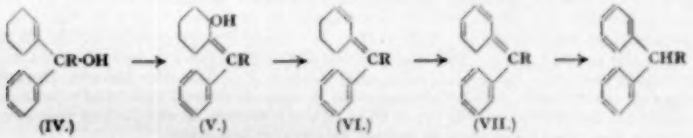


(I.) (II.) (III.)

dialkenyl ketones (cf. Part III), it did not form a semicarbazone. The ketone readily absorbed two moles of hydrogen in the presence of platinum oxide to give di*cyclo*hexyl ketone. The structures of the acid (II) and of the ketone (III) were also confirmed by their ultra-violet light absorption properties (see Table) characteristic of an $\alpha\beta$-ethylenic acid and of a di-$\alpha\beta$-unsaturated ketone, respectively. No indication was obtained of the formation of any unconjugated isomers, and the lithium metalation of the halide is thus not accompanied by any migration of the ethylenic double bond.

Whereas alkyl halides are often equally reactive towards lithium in hydrocarbon solvents and in ether (Gilman, Moore, and Baine, *J. Amer. Chem. Soc.*, 1941, **63**, 2479; Meals, *J. Org. Chem.*, 1944, **9**, 211), *cyclo*hexenyl chloride did not react appreciably with lithium in light petroleum (b. p. 60—80°). In the presence of benzaldehyde, the dehydration product (VI; R = H; see below) of the expected carbinol was obtained in small yield. It has been claimed (Wittig and Harborth, *Ber.*, 1944, **77**, *B*, 306) that *cyclo*hexenyl-lithium is an intermediate in the formation of phenyl*cyclo*hexene from *cyclo*hexenyl chloride and phenyl-lithium, but as has already been pointed out (Part I) evidence in support of this assertion appears to be lacking.

Preparation, Rearrangement, and Dehydration of cyclo*Hexenylphenyl- and* cyclo*Hexenyldiphenyl-carbinol.*—*cyclo*Hexenyl-lithium in ethereal solution condensed smoothly with benzaldehyde to give *cyclo*hexenylphenylcarbinol (IV; R = H), a high-boiling liquid, in 40% yield. The structure of the carbinol is proved by its ultra-violet light absorption properties, which are similar to those of benzyl alcohol, and by its hydrogenation to *cyclo*hexylphenylcarbinol. On treatment with dilute hydrochloric acid in aqueous acetone (IV; R = H) readily underwent the expected oxotropic rearrangement (cf. Braude, Jones, and Stern, *J.*, 1946, 396; Braude and Timmons, Part I) to give 2-benzylidene*cyclo*hexanol (V; R = H), a low-melting solid, which was characterised by the *p*-nitrobenzoate and exhibits ultra-violet light absorption properties typical of styryl derivatives (see Table). On distillation from potassium hydrogen sulphate, the *cyclo*hexanol was dehydrated, though incompletely, to 3-benzylidene*cyclo*hexene (VI; R = H), which exhibits ultra-violet light absorption properties typical of a 1-phenylbutadiene (see Table). Finally, the diene (VI) was dehydrogenated, either by bromination with *N*-bromosuccinimide followed by dehydrobromination with diethylaniline or, in better yield, by heating at 200° with palladised charcoal (Linstead and Thomas, *J.*, 1940, 1127) to diphenylmethane, the hypothetical intermediate triene (VII; R = H) undergoing immediate prototropic rearrangement to the fully benzenoid hydrocarbon. The diene (VI; R = H) was also obtained in low yield (20%) when lithium, *cyclo*hexenyl chloride, and benzaldehyde reacted together in refluxing light petroleum (b. p. 60—80°), the intermediate lithium derivative of the carbinol (IV; R = H) possibly eliminating lithium hydroxide under these conditions.



(IV.) (V.) (VI.) (VII.)

In a similar manner, condensation of *cyclo*hexenyl-lithium with benzophenone afforded the solid *cyclo*hexenyldiphenylcarbinol (IV; R = Ph) in 65% yield. Unlike the monophenyl derivative, it could not be hydrogenated over a platinum oxide or a palladium–calcium carbonate catalyst at ordinary pressure, or over a Raney nickel catalyst at 20 atmospheres, presumably owing to " catalyst hindrance " imposed by the additional phenyl group (cf. Linstead *et al.*,

J. Amer. Chem. Soc., 1942, **64**, 1985). On treatment with dilute hydrochloric acid in aqueous acetone, the carbinol underwent rapid oxotropic rearrangement to 2-benzhydrylidene-*cyclo*hexanol (V; R = Ph) which is readily dehydrated to 3-benzhydrylidene*cyclo*hexene (VI; R = Ph). The *cyclo*hexanol (V; R = Ph), which was characterised as the 3 : 5-dinitrobenzoate, exhibits ultra-violet light absorption similar to 1 : 1-diphenylethylene (see Table) and, on ozonisation, affords benzophenone in good yield. The diene (VI; R = Ph) also exhibits the expected light absorption properties and is smoothly dehydrogenated by palladised charcoal at 200° to triphenylmethane.

Preparation and Rearrangement of cyclo*Hexenylvinyl- and* cyclo*Hexenylpropenyl-carbinol.*—Condensation of *cyclo*hexenyl-lithium with acraldehyde or crotonaldehyde afforded the expected carbinols (VIII; R = H or Me) in 45% and 60% yields, respectively. Their constitution was confirmed by the lack of high-intensity light absorption in the 2300-A. region and, in the case of *cyclo*hexenylvinylcarbinol, by catalytic hydrogenation to *cyclo*hexylethylcarbinol, followed by oxidation of the latter to *cyclo*hexyl ethyl ketone.

On treatment with dilute acids, the carbinols (VIII) are converted into conjugated isomers which exhibit high-intensity maxima near 2350 A. The oxotropic rearrangement could theoretically give rise to two isomers (IX) and (X), depending on whether the hydroxyl group migrates into the ring or along the side chain. It was shown in Part II that, in the acyclic series, the hydroxyl group in an unsymmetrical dialkenylcarbinol migrates initially to the more highly substituted γ-carbon atom. It would, therefore, be expected that the first rearrangement product of *cyclo*hexenylvinylcarbinol (VIII; R = H) should be (IX; R = H) rather than (X; R = H). This is found to be the case, 2-allylidene*cyclo*hexanol (IX; R = H) being the sole product obtained on rearrangement in aqueous acetone containing hydrochloric acid. The structure of 2-allylidene*cyclo*hexanol was established by catalytic hydrogenation to 2-*n*-propyl*cyclo*hexanol and oxidation of the latter to 2-*n*-propyl*cyclo*hexanone. An authentic sample of the ketone was prepared by treating *cyclo*hexanone with *n*-propyl bromide in the presence of potassium *tert.*-butoxide under conditions recommended by Johnson *et al.* (*J. Amer. Chem. Soc.*, 1948, **70**, 3021; 1949, **71**, 1384) for the Stobbe condensation, and was characterised as the 2 : 4-dinitrophenylhydrazone.

With *cyclo*hexenylpropenylcarbinol (IX; R = Me), both γ-carbon atoms can be regarded as monoalkyl-substituted, but the electron accession at the γ-carbon atom in the ring will be smaller than that at the γ-carbon atom in the side chain, since the hyperconjugative effect of a methyl group is larger than that of any other alkyl group. Moreover, migration into the ring would be expected to be impeded by the strain accompanying the formation of an exocyclic double bond. This factor is evidently not one of predominant influence, since it does not prevent the formation of (IX) rather than (X) from the lower homologue, *cyclo*hexenylvinylcarbinol; but it may contribute in determining the direction of rearrangement in *cyclo*hexenylpropenylcarbinol where the alkyl substitution of the two γ-carbon atoms is more evenly balanced. In agreement with these considerations, *cyclo*hexenylpropenylcarbinol rearranges in aqueous acetone containing hydrochloric acid to 4-*cyclo*hex-1′-enylbut-3-en-2-ol (X; R = Me), the constitution of which was proved by Oppenauer oxidation to 4-*cyclo*hex-1′-enylbut-3-en-2-one (XI; R = Me), a lower homologue of β-ionone recently synthesized by two other routes by Heilbron, Jones, Richardson, and Sondheimer (*J.*, 1949, 737). A considerable proportion of the di-ether of (X; R = Me) is also formed. Self-etherification of this type has also been observed in several other related cases (cf. Heilbron, Jones, and Weedon, *J.*, 1945, 81; Braude, Fawcett, and Newman, *J.*, 1950, 793); further rearrangement in aqueous ethanol instead of aqueous acetone gives only the ethyl ether of (X; R = Me). Kinetic studies of the various rearrangements described in this paper are in progress and will be reported separately.

The ultra-violet light absorption properties of the various derivatives are collected in the Table, together with data for appropriate reference compounds.

The extension of this work to other cyclic lithium alkenyls (particularly *cyclo*pentenyl- and alkylated *cyclo*hexenyl-lithium derivatives) and their application to the synthesis of terpenoid compounds is now under investigation.

	$\lambda_{max.}$ A.*	$\varepsilon_{max.}$
*cyclo*Hexene-1-carboxylic acid (I)	2120	11,000
Crotonic acid	2000	10,000 [b]
Di*cyclo*hexenyl ketone (II)	2420	14,800
	3190	90
Dipropenyl ketone	2480	16,500 [c]
	3360	80
2-Benzylidene*cyclo*hexanol (V; R = H)	2430	14,200
β-Methylstyrene	2460	12,000 [d]
2-Benzhydrylidene*cyclo*hexanol (V; R = Ph)	2400	13,200
1 : 1-Diphenylethylene	2500	11,000 [e]
3-Benzylidene*cyclo*hexene (VI; R = H)	2230	7,700
	2810	18,700
1-Phenylbutadiene	2230	12,000 [b]
	2800	28,300
3-Benzhydrylidene*cyclo*hexene (VI; R = Ph)	2260	14,800
	2810	22,000
2-Allylidene*cyclo*hexanol (IX; R = H)	2330	27,000
Allylidene*cyclo*hexane	2365	8,000 [c]
4-*cyclo*Hex-1-enylbut-3-en-2-ol	2350	23,000
1-Vinyl*cyclo*hexene	2300	8,500 [d]

* Main maxima in ethanol solution.

[a] Mohler and Lohr, *Helv. Chim. Acta*, 1938, **21**, 485 (in water). [b] Braude and Coles, Part V (to be published). [c] Ramart-Lucas and Amagat, *Bull. Soc. chim.*, 1932, **51**, 108. [d] Arends, *Ber.*, 1931, **64**, 1936. [e] Braude, Jones, and Stern, *J.*, 1947, 1087. [f] Booker, Evans, and Gilliam, *J.*, 1940, 1453.

Experimental.

(M.p.s were determined on a Kofler block and are corrected.)

cyclo*Hex*-1-*enyl-lithium*.—1-Chloro*cyclo*hexene of high purity is required. Although the chloride has been obtained by several workers (Skita and Ritter, *Ber.*, 1911, **44**, 674; Favorski, *J. Gen. Chem. Russia*, 1936, **6**, 720; Bloomfield, *J.*, 1944, 114; Mousseron, Winternitz, and Jacquier, *Compt. rend.*, 1946, **223**, 36), its preparation does not appear to have been adequately described. *cyclo*Hexanone (250 ml.) was added, during 1—2 hours, to high-grade phosphorus pentachloride (500 g.) contained in a 1-l. flask, the flask being cooled in ice-water and frequently shaken. Next day, the contents of the flask were added drop-wise to water (3 l.) and the mixture was extracted with ether (1 l.). The ethereal solution was dried ($CaCl_2$), the ether removed by distillation, and the product fractionated, to give the chloride as a colourless liquid (180 g., 60%), b. p. 95°/160 mm., n_D^{25} 1·4798. It gives no immediate precipitate with alcoholic silver nitrate, but decomposes slowly when kept at room temperature, and must be refractionated immediately before use.

For the metalation, the freshly-distilled chloride (58 g., 0·5 mol.) was added slowly to a stirred suspension of finely-cut lithium (6·9 g., 1 mol.) in sodium-dried ether (1 l.) under nitrogen. Reaction set in after an induction period of *ca.* ½—1 hour, the solution becoming slightly turbid. A little later, the solution assumed a greenish or bluish colour. Stirring was continued overnight, almost the whole of the metal being consumed. A small amount of unchanged *cyclo*hexenyl chloride (not exceeding 5%) was usually recovered from subsequent condensations.

cyclo*Hexene*-1-*carboxylic Acid* (I) *and Di*(cyclo*hex*-1-*enyl*) *Ketone* (III).—Excess of solid carbon dioxide (300 g.) was added to a solution of *cyclo*hexenyl-lithium (from Li, 6·9 g.) in ether. After being stirred overnight, the solution was acidified with dilute aqueous hydrochloric acid. The ethereal layer was separated and extracted with aqueous sodium carbonate. The alkaline extract was acidified and the *cyclo*hexene-1-carboxylic acid (3 g., 5%) which separated was crystallised from light petroleum (b. p. 60—80°) and then had m. p. 37° (von Auwers and Krullpfeiffer, *Ber.*, 1915, **48**, 1396, give m. p. 38—39°). Light absorption in ethanol: Max. 2120 A., ε = 11,000; inflections 2070 and 2170 A., ε = 8,000 and 10,500, respectively. The amide separated from water in plates, m. p. 136° (Found: C, 66·6; H, 8·8; N, 11·0. Calc. for $C_7H_{11}ON$: C, 67·2; H, 8·8; N, 11·2%) (Einhorn, *Ber.*, 1893, **26**, 457, gives m. p. 127°).

The ethereal solution was evaporated to give *di*(cyclo*hex*-1-*enyl*) *ketone*, which separated from light petroleum (b. p. 60—80°) in stout, colourless prisms, m. p. 50° (Found: C, 82·3; H, 9·8. $C_{13}H_{18}O$ requires C, 82·2; H, 9·5%). Light absorption: see Table. The 2 : 4-*dinitrophenylhydrazone* was chromatographed on alumina from benzene–chloroform and, after crystallisation from methanol, had m. p. 159° (transition at 147°) (Found: C, 61·0; H, 6·0; N, 15·3. $C_{19}H_{22}O_4N_4$ requires C, 61·6; H, 6·0; N, 15·1%). Light absorption in chloroform: Max. 2560 (ε = 15,500) and 3880 A. (ε = 30,000). No semicarbazone was obtained under the usual conditions.

Hydrogenation of the ketone (3·7 g.) in ethyl acetate (50 ml.) in the presence of platinic oxide resulted in the uptake of 900 ml. of hydrogen at 17°/766 mm. (Calc., 950 ml.), giving di*cyclo*hexyl ketone (3 g.), b. p. 103°/0·3 mm., n_D^{25} 1·4891. The oxime, crystallised from ethanol, had m. p. 164° (Gauerka and Marvel, *J. Amer. Chem. Soc.*, 1928, **50**, 1180, give 158—160°) and the semicarbazone, crystallised from aqueous alcohol, had m. p. 195—196° (Danilow and Venus-Danilowa, *Ber.*, 1929, **62**, 2660, give m. p. 195°).

*cyclo**Hexenylphenylcarbinol*** (IV; R = H).—Freshly distilled benzaldehyde (5·3 g., 0·5 mol.) in ether (50 ml.) was added during 1 hour to a solution of *cyclo*hexenyl-lithium (from Li, 6·9 g.) in ether at 0°. After the mixture had been stirred overnight, saturated aqueous ammonium chloride (550 ml.) was added. The ethereal layer was separated, dried (Na_2SO_4–K_2CO_3), and worked up in the usual manner to give *cyclo**hexenylphenylcarbinol*** (36 g., 40%), b. p. 116°/2 × 10^{-4} mm., n_D^{18} 1·5589 (Found: C, 83·2; H, 8·8. $C_{19}H_{16}O$ requires C, 83·0; H, 8·5%). Light absorption in ethanol: Max. 2450 A., ε = 1,700.

Hydrogenation of the carbinol (3·4 g.) in ethyl acetate (50 ml.) in the presence of platinic oxide resulted in the uptake of 420 ml. of hydrogen at 18°/768 mm. (Calc., 450 ml.) to give *cyclo*hexylphenylcarbinol (3 g.), b. p. 128°/2 mm., which solidified when kept and crystallised from pentane in colourless prisms, m. p. 38—40° (Sabatier and Mailhe, *Compt. rend.*, 1904, **139**, 345, give m. p. 41°).

2-*Benzylidene*cyclo*hexanol* (V; R = H).—A solution of *cyclo*hexenylphenylcarbinol (4 g.) in 60% aqueous acetone (100 ml.) containing hydrochloric acid (0·1M.) was kept for 18 hours at room temperature. After neutralisation with aqueous potassium carbonate solution, the acetone was distilled off through a column, and the residue extracted with ether. Fractionation of the ethereal extract afforded **2-*benzylidene*cyclo*hexanol*** (3·5 g.), b. p. 110°/10^{-3} mm., which solidified when kept and crystallised from aqueous methanol in colourless needles, m. p. 62° (Found: C, 82·9; H, 8·8. $C_{19}H_{18}O$ requires C, 83·0; H, 8·5%). Light absorption in ethanol: see Table. The p-*nitrobenzoate* crystallised from light petroleum (b. p. 60—80°) and had m. p. 124° (Found: N, 4·3. $C_{26}H_{23}O_4N$ requires N, 4·2%).

3-*Benzylidene*cyclo*hexene* (VI; R = H).—(*a*) The above carbinol was distilled from potassium hydrogen sulphate in a high vacuum. The product was again distilled from potassium hydrogen sulphate, to give **3-*benzylidene*cyclo*hexene***, b. p. 81°/10^{-4} mm., n_D^{18} 1·6190 (Found: C, 91·5; H, 8·5. $C_{19}H_{18}$ requires C, 91·7; H, 8·3%). Light absorption: see Table.

(*b*) 1-Chloro*cyclo*hexene (29 g., 0·25 mol.), lithium (3·5 g., 0·5 mol.) and benzaldehyde (27·5 g.) in sodium-dried light petroleum (b. p. 60—80°) (500 ml.) were stirred for 20 hours in an atmosphere of nitrogen. Only 3-benzylidene*cyclo*hexene (8 g., 20%) was obtained.

Diphenylmethane.—(*a*) 3-Benzylidene*cyclo*hexene (1 g.) was refluxed with *N*-bromosuccinimide (4 g.) and benzoyl peroxide (20 mg.) in carbon tetrachloride (70 ml.) for 3 hours, and the resulting dibromide was heated with diethylaniline (5 ml.) for 1 hour at 100°. The impure diphenylmethane (0·3 g.) thus obtained was oxidised with potassium dichromate in sulphuric acid to benzophenone (2 : 4-dinitrophenylhydrazone, m. p. 238—239°, undepressed on admixture with an authentic specimen).

(*b*) 3-Benzylidene*cyclo*hexene (1 g.) was heated with a palladium–charcoal catalyst (0·3 g.; Linstead and Thomas, *J.*, 1940, 1127) at 200° for 22 hours in a slow stream of nitrogen. On ether-extraction, diphenylmethane (0·6 g.) was isolated and converted into benzophenone 2 : 4-dinitrophenylhydrazone, m. p. 238—239°, as above.

*cyclo**Hexenyldiphenylcarbinol*** (IV; R = Ph).—Benzophenone (9·1 g.) in ether (200 ml.) was added to *cyclo*hexenyl-lithium (from Li, 6·9 g.) in ether at 0°. After 18 hours' stirring, saturated aqueous ammonium chloride solution (500 ml.) was added and the ethereal layer was separated and dried. On removal of the ether, the residue solidified and, after being washed once with light petroleum (b. p. 60—80°), crystallised from aqueous ethanol to give *cyclo**hexenyldiphenylcarbinol*** (58 g., 60%) as white prisms, m. p. 134—135° (Found: C, 86·1; H, 7·8. $C_{25}H_{24}O$ requires C, 86·4; H, 7·6%). Light absorption in ethanol: Max. at 2560, 2580, and 2640 A., ε = 420, 450, and 345. A solution of the carbinol in benzene assumes a deep yellow colour on addition of one drop of concentrated sulphuric acid.

The carbinol was not hydrogenated in methanol in the presence of platinic oxide or a palladium–charcoal catalyst at ordinary pressure, or with a Raney nickel catalyst at 20 atmospheres' pressure.

2-*Benzhydrylidene*cyclo*hexanol* (V; R = Ph), **2-*Benzhydrylidene*cyclo*hexene*** (VI; R = Ph), ***and Triphenylmethane.***—The above carbinol (3 g.) was dissolved in 80% aqueous acetone (100 ml.) containing hydrochloric acid (0·1M.) and the solution set aside for 18 hours at room temperature. The solution was neutralised with aqueous potassium carbonate, the acetone removed by distillation through a column, and the residue extracted with ether. The ether was evaporated off, and the oil which remained was extracted with a little pentane. The insoluble portion of **2-*benzhydrylidene*cyclo*hexanol*** crystallised from ethanol in colourless prisms, m. p. 110—111° (Found: C, 86·6; H, 7·7. $C_{25}H_{26}O$ requires C, 86·4; H, 7·6%). Light absorption: see Table. Ozonolysis of the carbinol (2 g.) in carbon tetrachloride (40 ml.) for 18 hours, followed by decomposition of the ozonide with boiling water (100 ml.) and zinc dust (3 g.), gave an oily product which on treatment with phenylhydrazine afforded only benzophenone phenylhydrazone (1·3 g., 62%), m. p. 138—139°, undepressed on admixture with an authentic specimen.

The pentane-soluble portion gave **3-*benzhydrylidene*cyclo*hexene*** (1 g.), which crystallised from aqueous ethanol as a pale yellow solid, m. p. 67—68° (Found: C, 92·3; H, 7·4. $C_{25}H_{24}$ requires C, 92·7; H, 7·3%). Light absorption: see Table. The hydrocarbon (0·8 g.) was heated with a palladium–charcoal catalyst (0·25 g.) at 200° for 20 hours, as described above. Extraction with hot light petroleum (b. p. 80—100°) afforded triphenylmethane, m. p. 92·5°, undepressed on admixture with an authentic specimen.

*cyclo**Hexenylvinylcarbinol*** (VIII; R = H).—Acraldehyde (2·8 g., 0·5 mol.) in ether (30 ml.) was slowly added to *cyclo*hexenyl-lithium (from Li, 6·9 g.) in ether at 0°. Stirring was continued for 1 hour at room temperature and the products were worked up in the usual manner. After separation of a considerable quantity of solid polymeric material, *cyclo**hexenylvinylcarbinol*** (26 g., 40%) was obtained as a colourless liquid, b. p. 94°/13 mm., 67°/0·4 mm., n_D^{22} 1·4986 (Found: C, 78·3; H, 10·3. $C_8H_{14}O$ requires C, 78·3; H, 10·2%). Light absorption in ethanol: ε < 200 in the region 2200—4000 A.

1-cyclo*Hexylpropan*-1-*ol*.—Hydrogenation of *cyclo*hexenylvinylcarbinol (9·45 g.) in absolute ethanol (60 ml.) in the presence of platinic oxide resulted in the uptake of 3200 ml. of hydrogen at 17°/760 mm. (Calc., 3300 ml.) to give 1-cyclo*hexylpropan*-1-*ol* (8·5 g.), b. p. 88°/16 mm., n_D^{19} 1·4662 (Found: C, 75·6;

H, 12·5. $C_9H_{16}O$ requires C, 76·1; H, 12·7%). The carbinol (5 g.) was oxidised with potassium dichromate in sulphuric acid to *cyclo*hexyl ethyl ketone (3 g.), b. p. 82°/16 mm., n_D^{25} 1·4528 (Colonge and Duroux, *Bull. Soc. chim.*, 1940, **7**, 459, give b. p. 79°/9 mm.). The ketone was identified by the oxime, m. p. 70—72° (Colonge and Duroux give m. p. 72°), and by the semicarbazone, m. p. 184° (Colonge and Duroux give 181°).

2-*Allylidene*cyclo*hexanol* (IX; R = H).—A solution of *cyclo*hexenylvinylcarbinol (10 g.) in 60% aqueous acetone (200 ml.) containing hydrochloric acid (0·025*N*.), kept for 18 hours at room temperature, gave 2-*allylidene*cyclo*hexanol* (7·5 g.) as a colourless liquid, b. p. 109°/16 mm., n_D^{25} 1·5340, which partly solidified on storage; it had m. p. 41—43° (Found: C, 78·5; H, 10·3. $C_9H_{14}O$ requires C, 78·3; H, 10·3%). Light absorption: see Table.

2-*n*-*Propyl*cyclo*hexanone*.—(*a*) Hydrogenation of 2-allylidene*cyclo*hexanol (2·45 g.) in ethyl acetate (15 ml.) and ethanol (15 ml.) in the presence of platinic oxide resulted in the uptake of 850 ml. of hydrogen at 18°/771 mm. (Calc., 900 ml.), to give 2-*n*-propyl*cyclo*hexanol, b. p. 88°/16 mm., n_D^{25} 1·4677 (Fujise, *Chem. Zentr.*, 1929, I, 2991, reported b. p. 84°/6 mm., n_D^{20} 1·4604). The alcohol was oxidised by potassium dichromate in sulphuric acid to 2-*n*-propyl*cyclo*hexanone, b. p. 80°/16 mm., n_D^{25} 1·4552 (Vavon and Anziani, *Bull. Soc. chim.*, 1927, **41**, 1642, give b. p. 84°/13 mm., n_D^{15} 1·4558). The ketone gave a semicarbazone, m. p. 118—121°, and a 2 : 4-dinitrophenylhydrazone, m. p. 153—154°, both undepressed on admixture with the authentic specimens described below.

(*b*) *cyclo*Hexanone (6 g.) and *n*-propyl bromide (8 g.) were added, in one lot, to a boiling solution of potassium *tert.*-butoxide (from potassium, 2·8 g.) in *tert.*-butanol. After 20 minutes, the solution was allowed to cool and then acidified with ice-cold hydrochloric acid. Isolation of the product in the usual manner afforded 2-*n*-propyl*cyclo*hexanone (2·5 g., 30%), b. p. 86°/16 mm., n_D^{25} 1·4502. The semicarbazone, crystallised from aqueous ethanol, had m. p. 116—118° (Found: C, 61·6; H, 9·7; N, 21·1. Calc for $C_{10}H_{19}ON_3$: C, 61·0; H, 9·5; N, 21·3%) (Vavon and Anziani, *loc. cit.*, give m. p. 134°; Dice, Loveless, and Cates, *J. Amer. Chem. Soc.*, 1949, **71**, 3546, give m. p. 119—120°). The 2 : 4-*dinitrophenylhydrazone* was chromatographed on alumina from benzene–chloroform and crystallised from ethyl acetate in red plates, m. p. 153—154° (Found: C, 56·4; H, 6·3; N, 17·6. $C_{15}H_{20}O_4N_4$ requires C, 56·3; H, 6·3; N, 17·6%). Light absorption in chloroform: Max. 3680 A., ε = 22,400.

cyclo*Hexenylpropenylcarbinol* (VIII; R = Me).—Freshly distilled crotonaldehyde (35 g., 0·5 mol.) in ether (50 ml.) was added to *cyclo*hexenyl-lithium (from Li, 6·9 g.) in ether at 0°. Stirring was continued for 26 hours and the product was worked up in the usual manner. cyclo*Hexenylpropenylcarbinol* (42 g., 55%) distilled as a colourless liquid, b. p. 88°/0·8 mm., n_D^{25} 1·4998 (Found: C, 78·7; H, 10·7. $C_{13}H_{14}O$ requires C, 79·0; H, 10·5%). Light absorption in ethanol: ε < 200 in the region 2200—4000 A.

Rearrangement of (VIII; R = Me).—A solution of the above carbinol (5 g.) in 60% aqueous acetone (100 ml.) containing hydrochloric acid (0·1*N*.) was set aside for 24 hours at room temperature. The products were fractionated to give 4-cyclo*hex*-1′-*enylbut*-3-*en*-2-*ol* (3 g.), b. p. 116°/16 mm., n_D^{25} 1·5250 (Found: C, 79·3; H, 10·7. $C_{10}H_{16}O$ requires C, 79·0; H, 10·5%), and the corresponding *ether* (1·5 g.), b. p. 130°/10^{-3} mm., n_D^{25} 1·5312 (Found: C, 83·8; H, 10·6. $C_{26}H_{38}O$ requires C, 83·9; H, 10·5%). The ether produced no effervescence with an ethereal solution of methylmagnesium iodide. Light absorption of the carbinol: see Table. Light absorption of the ether in ethanol: Max. 2320 A., ε = 28,000. [*Added*, 3.5.50. Since this paper was submitted, the above alcohol has been described by Chanley and Sobotka (*J. Amer. Chem. Soc.*, 1949, **71**, 4140) who give b. p. 90°/1·5 mm., n_D^{25} 1·5220, $\lambda_{max.}$ 2335 A., ε 24,300.]

Rearrangement of *cyclo*hexenylpropenylcarbinol in 60% aqueous ethanol containing hydrochloric (0·1*N*.) or acetic acid (0·1*N*.) resulted in the formation of the corresponding 2-*ethoxy*-4-cyclo*hex*-1′-*enylbut*-3-*ene* (6 g.), b. p. 107°/16 mm., n_D^{25} 1·5012 (Found: C, 79·7; H, 11·2. $C_{12}H_{20}O$ requires C, 80·0; H, 11·1%). Light absorption in ethanol: Max. 2350 A., ε = 23,000.

4-cyclo*Hex*-1′-*enylbut*-3-*en*-2-*one* (XI; R = Me).—4-*cyclo*Hex-1′-enylbut-3-en-2-ol (4 g.), aluminium *tert.*-butoxide, dry benzene (200 ml.), and acetone (100 ml.) were refluxed for 30 hours. The product was worked up in the usual manner to give 4-*cyclo*hex-1′-enylbut-3-en-2-one (2 g.), b. p. 65°/0·1 mm., n_D^{17} 1·5401. It formed, in 90% yield, a 2 : 4-dinitrophenylhydrazone which was chromatographed on alumina from benzene–ethyl acetate and crystallised from ethyl acetate in deep-red prisms, m. p. 196—197°, undepressed on admixture with an authentic specimen (Heilbron, Jones, Richardson, and Sondheimer, *J.*, 1949, 737).

Attempted Formation of 1-cyclo*Hexenylsodium*.—1-Chlorocyclohexene (60 g., 0·5 mol.), sodium (23 g., 1 mol.), and benzophenone (46 g.) in ether (100 ml.) were stirred for 18 hours in an atmosphere of nitrogen, the solution being refluxed for part of the time. The solution assumed a deep blue colour owing to the formation of the ketyl, but most of the sodium remained undissolved. The solution was filtered and benzophenone (40 g.) was recovered. 1-Chloro*cyclo*hexene similarly failed to react with magnesium in ether.

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414. *The Mechanism of Oxidation of Monoethenoid Fatty Acids. Factors influencing Hydroperoxide Formation and Transition in Catalytic Autoxidations.*

By J. H. Skellon.

The formation and decomposition or transition of hydroperoxides during autoxidation of highly purified oleic acid under various conditions have been investigated. Ultra-violet light alone causes little or no direct hydroperoxide formation when the acid is exposed in a closed quartz cell or in benzene solution. In the presence of air and with limited humidity, small amounts of peroxide slowly develop. Aerial oxidation of oleic acid at room temperature in presence of strong ultra-violet light results in rapid formation of hydroperoxide, which then undergoes transition or decomposition. As with methyl esters, catalytic autoxidation of the free acid first results in an increased rate of peroxidation as the temperature increases, but hydroperoxide transition also increases, so that at the higher temperatures the maximum amount of peroxidation is much smaller.

The effects of metallic catalysts on *different stages* of oxidation have been examined. One group of metallic cations in the form of oil-soluble soaps exerts a maximum effect at the hydroperoxide transition stage, whilst another group is more efficient in the initial phases of oxidation.

Autoxidised oleic acid (in which hydroperoxide transition has occurred) containing metallic catalysts is again subject to slow peroxidation on storage with limited access to air and light.

Considerable progress has been made in recent years on problems connected with the elucidation of oxidation mechanisms in monoethenoid fatty acids. Formation and transition or decomposition of peroxidic oxygen during aerial oxidation of oleic and elaidic acids and their esters have been established by various authors (see, *inter al.*, Gunstone and Hilditch, *J.*, 1945, 836; Skellon, *J.*, 1948, 343; Skellon and Thruston, *J.*, 1949, 1626), whilst the general influence of catalysts was described by Skellon and Spence (*J. Soc. Chem. Ind.*, 1948, 242). Aerial oxidation of methyl oleate and elaidate in the presence of ultra-violet light at 35° yields the corresponding hydroperoxidic ester (Farmer and Sutton, *J.*, 1943, 119; Sutton, *J.*, 1943, 242). It appears that catalytic autoxidations may proceed according to specific mechanisms and there is evidence that the hydroperoxide transitions invariably afford ketonic derivatives.

Whilst the general efficiency of catalysts in gaseous autoxidations is known, little information is available about their intrinsic influence at different stages of these complex processes.

In the work now described, the stability of the initial hydroperoxide under varying external influences has been studied in detail, particularly effects of ultra-violet light, temperature, time, and catalyst.

Whilst ultra-violet light accelerated hydroperoxidation to a limiting value in aerial oxidations at room temperature, exposure of oleic acid, in closed quartz vessels or in benzene solution, to ultra-violet rays alone caused no appreciable peroxidation although there was evidence of change in configuration. However, previous exposure of unsaturated fatty acids to ultra-violet light reduced the induction period in subsequent aerial oxidations.

Comparison of catalytic autoxidations of oleic acid at 65° and 120° for short periods showed that first there was an increase in the rate of peroxidation at the higher temperature, followed by an increase in the rate of transition, with consequent smaller maxima of hydroperoxidic oxidation, again indicating that, in high-temperature catalytic autoxidations, hydroperoxide formation and transition take place more rapidly than, and possibly in a different way from, that at lower temperature. The present results show that metallic cations of different periodic groups may exert specific catalytic influence at the primary or the secondary stage of autoxidation of 120°. One group of typical metals (such as lead, aluminium, or barium) appears to accelerate the primary stage of peroxidation but has only a moderate effect on the transition stage. Another group, represented by thallium and zinc, has generally little catalytic activity which, however, is particularly marked at the transition stage to ketonic derivatives.

On the other hand, metals such as cobalt, vanadium, etc., appear to exert a positive effect at both the primary peroxidation and the transition stage, although maximum contents of peroxidic oxygen are small owing to continuous decomposition at 120°.

These results have provided valuable data for controlled autoxidation of monoethenoid fatty acids and may explain the varying activity of metallic "driers," which appears to be closely related to the atomic structure of the metal present as cation; according to Vold and Hattiangdi (*Ind. Eng. Chem.*, 1949, **41**, 2311) "drier" action is a maximum during early stages of autoxidation of ethenoid chains rather than at the final polymerisation.

Finally, fatty acids and esters catalytically autoxidised at 120° for short periods appear to be

susceptible to further slow changes on storage. Oleic acid, autoxidised for 7 hours at 120° (0·05% of metal catalyst) and subsequently left for long periods even in corked tubes with limited access to air and light, again slowly acquired an increased peroxidic-oxygen content, without gelation, whereas, in open dishes in films, the acid became viscous and even gelled. The increase in peroxidic-oxygen content on long storage may be caused by further slow saturation of residual ethenoid linkages, with little or no decomposition, consequent on the limited surface exposure to a minimum of air and light.

From these various observations it seems likely that the oily complexes present in the products of short thermal catalytic oxidations contain another type of peroxide not identifiable with the original hydroperoxide. Subsequent decomposition of such complexes by hydrolysis leads to a variety of scission products which appear to justify this view.

According to a mechanism of catalytic gaseous oxidation applicable to monoethenoid fatty acids and esters previously advanced (Skellon, *loc. cit.*), initially formed hydroperoxides are transformed in part into ketols, and further entry of oxygen affords mainly a monomeric oily product, little polymerisation occurring up to 10 hours. The oily product from methyl oleate had an approximate composition $C_{19}H_{34}O_4$ but liberated little iodine from potassium iodide.

Ellis (*Biochem. J.*, 1950, 129), as a result of more prolonged autoxidation of oleic and elaidic acids (45—100°), indicated that the products contained monoacyl derivatives of dihydroxystearic acid, α- and β-unsaturated keto-acids, and products of dimerisation and polymerisation containing β-keto-acids. He also isolated *cis*- and *trans*-11-ketoheptadec-8-ene-1-carboxylic acid (λ-keto-oleic and -elaidic acids) by chromic acid oxidation of ricinoleic acid (*J.*, 1950, 9), and considered that the autoxidations yielded successively olefinic acid, olefinic keto-acid, olefinic keto-peroxide, and peroxidation products (including an epoxide). Separate experiments on the autoxidation of this keto-oleic acid at 42° apparently gave high peroxide yields (27%) after 24 hours.

The results serve to emphasise the complexity of these autoxidations, which depend on external conditions. In this laboratory, work is continuing on *short* catalytic high-temperature autoxidations of pure monoethenoid fatty acids and derivatives, under conditions which it is hoped will prevent undue dimerisation or polymerisation.

Experimental.

Preparation of Pure Oleic Acid.—Oleic acid was prepared from olive oil (500 g.) by methods previously described (*J. Soc. Chem. Ind.*, 1931, **50**, 131T) (Found: I.V., 89·9, 89·8; equiv., 281·8, 282·2. Calc. for $C_{18}H_{34}O_2$: I.V., 90·1; equiv., 282).

Influence of Ultra-violet Light on Peroxide Formation in Mono-ethenoid Fatty Acids. Pure Oleic Acid.—Pure oleic acid, in quartz cells, was exposed to the full rays of a mercury-vapour lamp (i) in presence of a slow stream of oxygen, (ii) in open quartz cells with subsequent oxidation, (iii) with limited access to air, (iv) in closed quartz cells, and (v) in benzene solution. The results are given in Table I.

Table I.

Influence of ultra-violet light on peroxidic oxygen content of pure oleic acid.

1. Oleic acid exposed in open quartz vessel in presence of a slow stream of oxygen at room temp.:

Time of exposure (hrs.)	2	4	6	8	10	12
Peroxidic oxygen, found, % ...	0·43	0·50	1·06	0·65	0·57	0·50

	Peroxidic oxygen, found, %.
2. Oleic acid exposed for 10 hrs. in an open quartz cell. Subsequently oxidised for 7 hours at 120°	0·61
3. Oleic acid exposed in a flat dish of large surface area to direct rays for 48 hrs....	0·47
4. Oleic acid exposed in open quartz cell, with limited access to air, for 16 hrs. ...	0·04
5. Oleic acid exposed in a closed quartz cell, for 16 hrs.	0
6. Oleic acid in benzene solution in an open quartz cell, exposed for 8 hrs.	0

When oxygen was passed into oleic acid exposed to ultra-violet light at room temperature, the peroxidic-oxygen content rose to 1·06% in 6 hours, the acid thereafter commencing to undergo transition. Farmer and Sutton (*J.*, 1943, 119) found 0·64% of active oxygen on photochemical oxidation (4 hours) of methyl oleate at <35°.

Ultra-violet light, even in presence of a limited amount of air, caused development of small peroxidic-oxygen content. Subsequent aerial oxidation of 120° of such activated acid caused rapid peroxidation (Found after 7 hours: acid val., 176·1; I.V., 48·4; sap. val., 252·8; peroxidic oxygen, 0·64%). The effect of previous exposure to ultra-violet light thus gave an autoxidation product similar to that obtained by using catalysts such as benzoyl peroxide (0·5%) (Found: acid val., 160·9; I.V., 56·1; sap. val., 230·0; peroxidic oxygen, 0·51%) or blown whale oil (Found: acid val., 171·6; I.V., 42·4; peroxidic

oxygen, 0·517%). It may be noted, however, that the intrinsic effect of ultra-violet light in absence of air is minute.

Catalytic Oxidations. Catalyst Influence in Primary and Secondary Phases of Aerial Oxidation. Changes in Peroxidic-oxygen Content of Pure Oleic Acid during Autoxidation at 120°.—(a) *In presence of pure metallic soaps.* Catalysts used in the following experiments included oleates of Co, Pb, V, Al, Ba, Tl, and Zn, and cobalt linoleate and naphthenate. Preparations and analyses were by the following methods: preparation and analysis of cobalt and vanadium compounds (*J. Soc. Chem. Ind.*, 1948, **67**, 365); thallium oleate (Menzies, *J.*, 1924, 1148); barium oleate (*J. Soc. Chem. Ind.*, 1931, **50**, 131T). Oleates of lead, aluminium, and zinc were prepared by double decomposition from sodium oleate. Typical analysis of the oleates were: Co, 10·1 (calc. 9·5%); Pb, 25 (calc. 26·9%); V, 7·5 (calc. 8·1%); Al, 3 (calc. 3·1%); and Zn, 10·1% (calc. 10·3%).

TABLE II.

Catalyst influence on the rate of autoxidation of pure oleic acid (120°; 7 *hours*).

	Catalyst, 0·05% of metal as oleate.						
	Co.	Pb.	V.	Ba.	Tl.	Zn.	Al.
Maximum peroxidic-oxygen content, found, %	0·78	1·70	0·57	0·92	0·83	0·76	1·30
Time to attain above maximum peroxide content (hrs.)	6	2	5	5	5	5	2
Rate of increase of peroxidic-oxygen content (units per hr.)	0·15	0·85	0·11	0·18	0·17	0·15	0·65
Minimum peroxidic-oxygen content (7 hrs.), found, %	0·26	0·26	0·29	0·35	0·68	0·59	0·21
Rate of transition of peroxidic-oxygen content (units per hr.)	0·52	0·29	0·18	0·28	0·07	0·08	0·20
Iodine value (7 hrs.)	47·9	43·6	50·7	52·2	52·6	63·7	33·9
Rate of fall of iodine value (units per hr.)	6·0	6·6	5·6	5·4	5·4	3·8	8·0
Acid value (7 hrs.)	170·5	160·4	170·4	168·9	173·2	175·4	170·8
Rate of fall of acid value (units per hr.)	3·9	5·4	3·9	4·1	3·9	3·2	3·8

TABLE III.

Peroxidic-oxygen content, %.

Time (hrs.).	1	2	3	4	5	6	7
65°	—	0·09	—	0·87	0·32	—	0·21
120°	0·21	0·33	0·38	0·40	0·37	0·34	0·20
120° (second specimen of vanadium oleate)							0·16

TABLE IV.

Changes in perioxidic-oxygen content (%) *of previously oxidised oleic acid.*

Catalyst (0·05% of metal).	After oxidation.	After storage in loosely corked tubes for 15 months.	18—30 months.
Cobalt oleate (commercial)	0·02	0·39	—
Cobalt oleate (pptd.)	0	0·10	0·33 (30 months)
Cobalt linoleate (commercial)	0·02	0·47	—
Cobalt " tungate " (commercial)	0·04	0·35	—
Vanadium oleate II	0·16	0·49	0·66 (18 months)
Molybdenum oleate	0·21	0·27	—
Titanium oleate	0·19	0·94	—
Lead oleate	0·26	0·37	—
Nickel oleate	0·12	—	0·33 (30 months)
Copper oleate	0·36	0·57	—

(b) *Autoxidations.* Oxidation experiments were carried out in a glass vessel fitted with a Bakelite cover, with arrangements for efficient mixing and for temperature control (±1°) as previously described (Skellon, *loc. cit.*). Samples were withdrawn at regular intervals during oxidation for determination of acid value, iodine value, and peroxidic-oxygen content (iodometrically). The changes in peroxidic-oxygen content with a series of catalysts are illustrated in Table II, expressed as percentage of active oxygen (Calc. for $C_{18}H_{34}O_2$, 5·09%). The rates of decrease of acid value and iodine value during autoxidation are also given.

Influence of Temperature.—The results of catalytic oxidations of pure oleic acid at 65° and 120° are recorded in Table III, the catalyst being vanadium oleate (0·05% of metal).

At the lower temperature, peroxide formation was slower during the first 2 hours; after 4 hours it rapidly accelerated to twice the value obtained at 120°, thereafter diminishing rapidly.

Slow " After-effect " of Catalyst in Presence of a Limited Amount of Air and Light.—Autoxidised oleic acid (7 hours; 120°; 0·05% of metal as soap) was left in loosely corked tubes with limited access to air and light. Peroxidic-oxygen content was redetermined at intervals of 15—30 months. The results are recorded in Table IV.

In these conditions peroxidic-oxygen content increased, the change depending on the nature of the catalyst; with cobalt and other transition-metal cations, the amount of " after-effect " change was high. The conditions, it should be noted, were entirely different from those prevailing when unsaturated fatty acids or parent oils are exposed in films to excess of air and light, decomposition of peroxide then being followed by polymerisation and gelation.

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415. *Studies on Phosphorylation. Part VI. The Reaction between Organic Bases and Esters of the Oxy-acids of Phosphorus. An Interpretation based on a Comparison of Certain Aspects of the Chemistry of Sulphur and Phosphorus.*

By V. M. CLARK and A. R. TODD.

The monodebenzylation of neutral esters of phosphorous, phosphoric, and pyrophosphoric acids, containing one or more benzyl groups, by tertiary amines (Baddiley, Clark, Michalski, and Todd, *J.*, 1949, 815) has been extended to include all classes of amines. Debenzylation can also be brought about by base hydrochlorides. The influence of structure on the capacity of an amine to debenzylate such esters is discussed, and a general interpretation of the reactions involved is advanced based on a comparison with analogous reactions occurring among organic derivatives of the oxy-acids of sulphur.

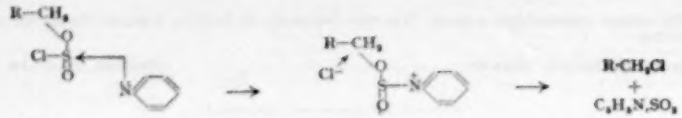
IN Part V of this series (Baddiley, Clark, Michalski, and Todd, *J.*, 1949, 815) it was shown that neutral esters of phosphorous, phosphoric, and pyrophosphoric acids, containing one or more benzyl groups, can be selectively monodebenzylated by reaction with a tertiary amine. This reaction has since been studied in some detail and has been extended to include a variety of bases including primary and secondary amines. The results of this study, which covers both the influence of structure on the capacity of an amine to bring about this reaction and the debenzylating action of base hydrochloride are now reported. A comparison of the behaviour of certain derivatives of the oxy-acids of sulphur with that of the phosphorus compounds under discussion has led to a general interpretation of the debenzylation reaction. For convenience in presentation, it is desirable to consider at the outset some of the reactions of the sulphur compounds.

There are many examples of the selective removal of one alkyl group from an alkyl ester of an oxy-acid of sulphur resulting from the use of the ester to alkylate an amine, or from hydrolysis, *i.e.*, the alkylation of the water molecule or the hydroxyl ion. Such dealkylation can result from solvolysis or from a bimolecular nucleophilic displacement, though the latter is more frequent (McCleary and Hammett, *J. Amer. Chem. Soc.*, 1941, **63**, 2254; Morgan and Cretcher, *ibid.*, 1948, **70**, 375). In the displacement reaction, the attacking entity (*e.g.*, a nitrogenous base, an alkoxyl or hydroxyl ion) seeks an electron-deficient point in the sulphur-containing molecule, and in particular, for alkylation to occur, the alkyl group, and not the sulphur atom, must be the centre for this attack. It is convenient to discuss the behaviour of the various classes of sulphur compounds separately.

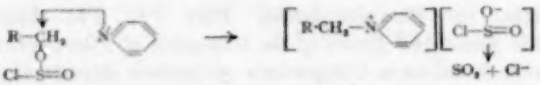
Quadrivalent Sulphur Compounds.—The dialkyl esters of sulphurous acid are very weak alkylating agents, being virtually unaffected by nitrogenous bases. Thus, Voss and Blanke (*Annalen*, 1931, **485**, 258) showed that aniline and pyridine were alkylated by dialkyl sulphites at room temperature only after several weeks, and even then the reaction was far from complete. By comparison, the alkyl chlorosulphinates (RO·SO·Cl), in which one of the alkoxyl groups of a dialkyl sulphite has been replaced by a chlorine atom, show greatly enhanced reactivity towards organic bases. The chlorine atom is a much more powerful electron-acceptor than the alkoxyl group it replaces and in consequence the central sulphur atom has an enhanced electrophilic character. Moreover, the inductive effect of the halogen atom is relayed to the α-carbon atom of the alkyl group, which thereby becomes a second centre for nucleophilic attack. This duality of positive centres in the chlorosulphinate molecule is implicit in the two mechanisms of decomposition which are observed in the presence of a tertiary base. Thus, Gerrard (*J.*, 1936, 688) observed that, on addition of pyridine to an alkyl chlorosulphinate in cold dry ether, a yellow oily mixture of 1-alkylpyridinium chloride and 1-alkylpyridinium chlorosulphinate separated in

quantity, leaving about 40% of alkyl chloride in the ethereal layer. To account for his observations, Gerrard put forward two mechanisms which are now represented thus :

Mechanism A



Mechanism B

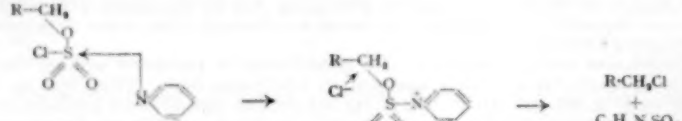


It should be noted that the above formulation of mechanism A represents the extreme case in which a chloride *ion* is actually liberated. The same products would be obtained were the attack of the chlorine atom on the alkyl group to be intramolecular and contemporaneous with the attack of the base on the sulphur atom. Mechanism A accounts for the formation of alkyl chloride and the liberation of sulphur dioxide, the base–SO_2 complex readily decomposing with continuous regeneration of the base. Such complexes have been isolated (Bateman, Hughes, and Ingold, *J.*, 1944, 243) and are known to decompose very readily into their components (Hoffman and Van der Werf, *J. Amer. Chem. Soc.*, 1946, **68**, 997; 1948, **70**, 262). This mechanism also receives support from the work of Kenyon, Lipscomb, and Phillips (*J.*, 1930, 415) on the replacement, by means of thionyl chloride, of the hydroxyl group in an optically active alcohol by a chlorine atom : in the absence of a tertiary base, optically active chlorosulphinates underwent decomposition to the chloride with retention of configuration, but, in the presence of a tertiary base, an intermediate was formed with liberation of chloride anions, these anions then taking up suitable positions for the production of the chloride with inversion of configuration. This is precisely what would be expected on the basis of mechanism A.

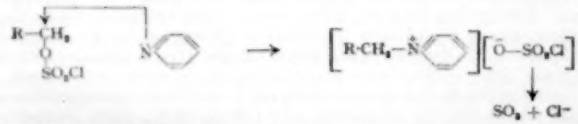
Mechanism B accounts for the isolation of the quaternary alkyl-pyridinium chloride, for it is inconceivable that this is formed by the addition of alkyl chloride to the base during the reaction. Combination of isoamyl chloride and pyridine in dry ether proceeds so slowly at room temperature that no deposit of salt occurs in three months, even when the solution is saturated with dry sulphur dioxide (Gerrard, *loc. cit.*).

Sexavalent Sulphur Compounds.—The alkyl chlorosulphonates would be expected to behave analogously to the alkyl chlorosulphinates, save that the sulphur atom, having an enhanced positive character relative to the α-carbon atom of the alkyl group, would be attacked in preference to, although not to the exclusion of, the alkyl group. Two reaction mechanisms are possible, *e.g.*, with pyridine :

Mechanism A



Mechanism B



In mechanism A, a base–SO_2 complex is formed, together with the alkyl chloride, whereas in mechanism B, the quaternary chlorosulphonate (or chloride) is formed. Both these mechanisms

have received experimental verification, for Willcox (*Amer. Chem. J.*, 1904, **32**, 446) obtained dimethylaniline–sulphur trioxide (in 83% yield), together with ethyl chloride, by treating ethyl chlorosulphonate with dimethylaniline in the cold (mechanism A) and also isolated a little of the quaternary dimethylethylanilinium chloride (mechanism B). Baumgarten (*Ber.*, 1926, **59**, 1166) obtained similar results using pyridine in place of dimethylaniline, and Binkley and Degering (*Proc. Indiana Acad. Sci.*, 1939, **49**, 117) found that they could obtain an alkyl halide and a base–SO_3 complex using dibutylamine; in the latter case, however, the complex, being in effect an amino-sulphonic acid, formed a salt with a further molecule of the secondary amine:

$$RO{\cdot}SO_2Cl + Bu_2NH \longrightarrow RCl + Bu_2NH,SO_3 \xrightarrow{Bu_2NH} [Bu_2NH_2^+][Bu_2N{\cdot}SO_3^-]$$

With respect to mechanism B, Traube (*Z. angew. Chem.*, 1925, **38**, 441) found that he could alkylate aniline using ethyl chlorosulphonate, and Delépine and Demars (*Bull. sci. pharmacol.*, 1923, **30**, 577) showed that methyl chlorosulphonate alkylated dimethylamine at 0°.

Effect of the Variation of R *on the Interaction of Bases with* RO·SO·Cl and RO·SO_2·R′.—When R is an aryl group, the carbon atom carrying the chlorosulphinate residue is no longer a centre for nucleophilic attack. The electrophilic character of the sulphur atom is also reduced. Thus, although the alkyl chlorosulphinates are decomposed by tertiary amines at room temperature, phenyl chlorosulphinate does not react with pyridine or quinoline below 120° (Gerrard, *J.*, 1940, 218). However, when R is aralkyl the chlorosulphinates are much less stable since the α-carbon atom of, *e.g.*, the benzyl group is predisposed to nucleophilic attack (cf. Hughes, *Trans. Faraday Soc.*, 1941, **37**, 627); benzyl chlorosulphinate decomposes at room temperature (Carré and Libermann, *Compt. rend.*, 1933, **196**, 1419).

In the light of the above evidence, the aryl esters of sulphonic acids would be expected to be very poor arylating agents, as indeed they are, the phenyl ester of toluene-*p*-sulphonic acid being unaffected by alcoholic ammonia at 190° (Freudenberg and Hess, *Annalen*, 1926, **448**, 121), whereas the corresponding methyl ester reacts in the cold (Autenreith and Bernheim, *Ber.*, 1904, **37**, 3800). However, by substituting the aryl nucleus with nitro-groups in the 2- and the 4-position, the carbon atom carrying the sulphonate residue becomes a centre for nucleophilic attack, and esters of this type are arylating agents (Ullmann and Nádai, *Ber.*, 1908, **41**, 1870). By increasing the nucleophilic character of the attacking reagent, it should be possible to cleave an aryl ester of a sulphonic acid without resorting to substitution with nitro-groups. In this case, the sulphur atom may be attacked in preference to the α-carbon atom, and Turner and his co-workers (*J.*, 1930, 928, 1853) showed that piperidine cleaved sulphonic esters with sulphonation rather than alkylation of the base:

$$Ar{\cdot}SO_2{\cdot}OR + C_5H_{10}NH \longrightarrow R{\cdot}OH + Ar{\cdot}SO_2{\cdot}N\langle\bigcirc\rangle$$

There is the interesting possibility of a mechanistic transition point inherent in these observations and, indeed, Bell (*J.*, 1931, 609) has reported that, whereas *o*-nitrophenyl toluene-*p*-sulphonate is cleaved by piperidine with acyl–oxygen fission, the corresponding 2 : 4-dinitrophenyl ester undergoes alkyl–oxygen fission (*cf.* Ullmann and Nádai, *loc. cit.*).

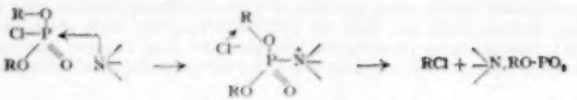
Phosphorus Compounds.—The decomposition of phosphorus compounds in the presence of bases has been examined in the light of the conclusions reached above regarding the behaviour of certain derivatives of the oxy-acids of sulphur. In Part V of this series (*loc. cit.*) we recorded experiments on the selective debenzylation of neutral esters of certain of the oxy-acids of phosphorus carried out in consequence of the observation of Atherton, Howard, and Todd (*J.*, 1948, 1106) that dibenzyl chlorophosphonate underwent rapid and complete decomposition with 4-methylmorpholine, leading to the formation of 4-benzyl-4-methylmorpholinium chloride, and, presumably, benzyl metaphosphate:

$$R_3N + (Ph{\cdot}CH_2{\cdot}O)_2POCl \longrightarrow [R_3N{\cdot}CH_2{\cdot}Ph]^+[Cl]^- + Ph{\cdot}CH_2{\cdot}O{\cdot}PO_2$$

On the other hand, Gerrard (*J.*, 1940, 1464), investigating the decomposition of alkyl chlorophosphonates and related compounds in the presence of tertiary bases, had obtained considerable yields of alkyl chloride. By analogy with the sulphur compounds, there are two mechanisms to be considered. The attacking nucleophilic reagent (the base) seeks an electrophilic centre which can be located either on the central phosphorus atom or on the α-carbon atom of one of the attached groups. If the phosphorus atom is the centre for the initial attack, then we have a

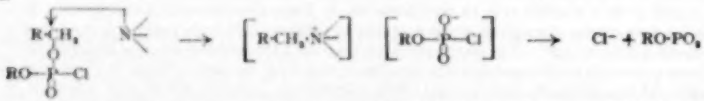
mechanism designated as type A, which results, in the case of a chlorophosphonate, in the formation of alkyl chloride and a base–metaphosphate complex (cf. Langheld, *Ber.*, 1911, **44**, 2076) :

Type A



If, however, the α-carbon atom of an attached group is the centre for the initial attack, then we get a mechanism designated as type B, which results in the formation of a quaternary halide, the base becoming alkylated :

Type B



This distinction leads to the conclusion that alkylation by a phosphorus compound is to be attributed more to the nature of the alkyl group than to the valency state of the phosphorus atom. Thus, as reported in Part V of this series (*loc. cit.*), trialkyl and triaryl phosphates are virtually unaffected by tertiary bases but, in particular, tribenzyl phosphate is affected, since the benzyl group is very susceptible to nucleophilic attack (*cf.* Hughes, *loc. cit.*; Baker, *Trans. Faraday Soc.*, 1941, **37**, 632).

If the electrophilic character of the phosphorus atom is increased by the replacement of one alkoxyl group of a trialkyl phosphate by a chlorine atom, the alkylating properties of the molecule are not enhanced; instead, we facilitate mechanism A relative to mechanism B, *i.e.*, increase the possibility of decomposition to alkyl chloride. The further replacement of a second alkoxyl group by a chlorine atom results in mechanism A being even more prominent and more rapid. Thus butyl dichlorophosphonite, $BuO{\cdot}POCl_2$, reacts with pyridine at 0° to give 31% of butyl chloride, whereas dibutyl chlorophosphonate, $(BuO)_2POCl$ only reacts with pyridine on heating (Gerrard, *loc. cit.*), and tributyl phosphate is unaffected when refluxed with a tertiary base.

We do not wish to imply that structural factors influencing mechanisms of type A are completely independent of those influencing mechanisms of type B. They are not, for an increase in the electrophilic character of the phosphorus atom does produce an increase in the electrophilic character of the α-carbon atoms of the attached alkoxyl groups—through induction; but the resultant enhancement of mechanism A usually outweighs any facilitation of mechanism B.

In Part V of this series, the results of the variation of substrate in the base/substrate ester reaction were recorded and it was noted that the esters of aminophosphonic acid were virtually unaffected under the normal reaction conditions and could be recovered in high yield. Presumably the nitrogen atom in, say, dibenzyl aminophosphonate, by accession of electrons from its lone pair, depresses the electrophilic reactivity not only of the central phosphorus atom but also of the benzyl groups, so that debenzylation of an aminophosphonate under the usual conditions of reaction would only be possible if the tendency of the nitrogen atom to donate electrons to the phosphorus atom were reduced.

The removal of only one benzyl group from tribenzyl phosphate by reaction with a tertiary base is almost certainly related to the relative unreactivity of the aminophosphonates, the integral negative charge of the anion produced on monodebenzylation reducing the overall electrophilic character of the molecule and thereby inhibiting further reaction.

Atherton, Howard, and Todd (*loc. cit.*) investigated the stability of dibenzyl chlorophosphonate in the presence of various bases, estimating the unchanged material after a specified time by passing ammonia into the mixture and isolating the dibenzyl aminophosphonate produced. It was noted that the heterocyclic bases substituted in the 2-position were markedly better than pyridine for purposes of phosphorylation using dibenzyl chlorophosphonate. The present investigation has shown that the capacity of heterocyclic bases to cause debenzylation is markedly impaired by substitution in the α-positions to the heterocyclic nitrogen. Thus, in a series of experiments using tribenzyl phosphate as substrate and carrying out the reactions under standard conditions (2 hours at 100°) the following results were obtained :

Base.	Yield (%) of dibenzyl hydrogen phosphate.	Recovery (%) of tribenzyl phosphate.
4-Methylmorpholine	65	10
Morpholine	50	10
Pyridine	62	2
Quinoline	63	22
2-Picoline	20	56
2 : 6-Lutidine	8	73
Quinaldine	5	83

When the temperature of reaction was raised to 115—116°, the yield of monodebenzylated material afforded by 4-methylmorpholine rose to 87%, whereas the yield afforded by pyridine remained virtually constant at 61—62%. The marked difference in behaviour between pyridine and quinoline and their 2-substituted homologues cannot be attributed to any difference in basic strength in the generally accepted sense, *i.e.*, basic strength determined with respect to hydrogen ion, for with this as the reference acid, 2 : 6-lutidine ($K_b = 1 \times 10^{-7}$) is a stronger base than pyridine ($K_b = 2{\cdot}3 \times 10^{-9}$), yet its power to debenzylate tribenzyl phosphate is very much less. This contrast in the behaviour of pyridine and 2 : 6-lutidine parallels that observed by Brown, Schlesinger, and Cardon (*J. Amer. Chem. Soc.*, 1942, **64**, 325), who showed that, although 2 : 6-lutidine is a stronger base than pyridine when competing for hydrogen chloride, it is displaced by pyridine from its boron trifluoride adduct. Moreover, whereas pyridine forms an adduct with trimethylboron, 2 : 6-lutidine fails to do so even at temperatures as low as −80°. In the same way, 2-picoline, a stronger base than 4-picoline, is nevertheless much less effective as a debenzylating agent. This is in keeping with the lower stability of its trimethylboron adduct (Brown and Barbaras, *ibid.*, 1947, **69**, 1137). The American workers attribute their results to a steric effect (*cf.* also Van der Werf, Davidson, and Michaelis, *ibid.*, 1948, **70**, 908) and we consider that the same factors operate in the debenzylation reaction, *i.e.*, that the reluctance of the *ortho*-substituted pyridines and quinolines to participate is mainly due to steric strain in the transition complex.

It is of interest to compare the relative efficacies of aniline and its *N*-methyl derivatives as debenzylating agents. There is little difference between the basic strengths of aniline, methylaniline and dimethylaniline, but whereas the product of the reaction of tribenzyl phosphate with the tertiary amine is a quaternary salt the products formed in the cases of aniline and methylaniline are salts of weak bases with a strong acid, *i.e.*, as the reaction progresses in aniline or methylaniline solution, hydrogen ions may be formed and may facilitate solvolysis of the phosphate ester. Such an explanation would account for the anomalous behaviour of dimethylaniline, for, whereas tribenzyl phosphate is debenzylated to give dibenzyl hydrogen phosphate in high yield in aniline or methylaniline solution (after 2 hours at 100° the yields are 79% and 75% respectively), in dimethylaniline solution after the same length of time at 100°, 65% of the starting material can be recovered unchanged.

All our experimental observations are, of course, qualitative; detailed conclusions about subtleties in the reaction mechanism cannot be drawn since all reactions were carried out using the basic component as solvent. Moreover, the isolation of product and recovery of starting material are procedures which do not lend themselves easily to exact analysis. Again, side reactions may creep in and obscure certain details. For example, in pyridine solution, the yield of dibenzyl hydrogen phosphate from tribenzyl phosphate after 15 minutes at 100° is 55%, after 1 hour 85%, and after 2 hours only 62%. This must mean that dibenzyl hydrogen phosphate is itself affected by base, and indeed, when this acid is refluxed in pyridine solution for 6 hours, only 44% of the acid is recoverable unchanged, at least 22% of the original phosphorus being isolated as inorganic phosphate. Similarly, if dibenzyl hydrogen phosphate is heated for 2 hours at 100° in dimethylaniline, only 70% is recoverable unchanged and, if the period of heating is extended to 6 hours, the recovery drops to 58%. This debenzylation of dibenzyl hydrogen phosphate in tertiary base solution is probably due to factors similar to those which operate in the reaction between tribenzyl phosphate and aniline or methylaniline. Despite their qualitative nature, however, our results do give a general picture of the main reactions involved since, although the differences observed in the behaviour of various bases may really only be differences in degree, they are so large as to be tantamount in practice to differences in kind. From a practical standpoint it would appear that, although amines of all types may be used, the tertiary aliphatic amines give the highest yields in monodebenzylation reactions. Moreover, in phosphorylation reactions using dibenzyl chlorophosphonate, decomposition of the reagent by the base is reduced to a minimum if 2 : 6-lutidine is employed.

In the course of the investigations described in this series of papers, reference has been made

on occasion to the possibility of debenzylation by the action of a base hydrochloride; in particular, it has been suggested that the extensive decomposition of dibenzyl chlorophosphonate during certain phosphorylation reactions carried out with pyridine or 2 : 6-lutidine as solvent was in part attributable to the base hydrochloride produced in the course of the reaction.

In the decomposition of chlorophosphonates we should, as mentioned above, expect a mechanism of type A to play a more important part than it does in the decomposition of triaralkyl phosphates. Moreover, the attacking chloride anion in the postulated second stage of mechanism A need not arise from within the molecule undergoing decomposition—it could be introduced from an external source.

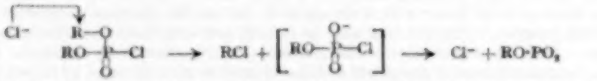
On examining the action of pyridine and 2 : 6-lutidine on tribenzyl phosphate in the absence and presence of their respective hydrochlorides it was found that the yield of monodebenzylated material was markedly increased by the introduction of 2 : 6-lutidine hydrochloride into the 2 : 6-lutidine reaction mixture. Thus, with a reaction time of 2 hours at 100° the following results were obtained:

Debenzylating agent.	Yield (%) of dibenzyl hydrogen phosphate.	Recovery (%) of tribenzyl phosphate.
Pyridine	62	2
Pyridine + its hydrochloride	61	4
2 : 6-Lutidine	5	75
2 : 6-Lutidine + its hydrochloride	31	46

Similar experiments in which the phosphate was heated in ethoxyethanol solution with base hydrochloride alone gave the following results:

Debenzylating agent.	Yield (%) of dibenzyl hydrogen phosphate.	Recovery (%) of tribenzyl phosphate.
Pyridine hydrochloride	52	32
2 : 6-Lutidine hydrochloride	55	28

These results show quite definitely that debenzylation occurs, not only as a result of attack by a nitrogenous base, but also by the attack of chloride ion, and this being so it is apparent that the decomposition of chlorophosphonate, according to a mechanism of type A, is catalysed by traces of base hydrochloride. Thus,



On the basis of the above considerations, it is clearly advantageous to work up phosphorylation reactions using dibenzyl chlorophosphonate as soon as possible.

The preparation of dibenzyl hydrogen phosphate (Atherton, Howard, and Todd, *loc. cit.*) has been re-examined in the light of our present knowledge, and a new and more convenient method has been devised for its preparation in bulk by adaptation of the phosphorylation method using dibenzyl phosphite in carbon tetrachloride solution in presence of a tertiary base (Atherton and Todd, *J.*, 1947, 674). In this adaptation the substance to be phosphorylated is replaced by the water molecule, and the tertiary amine by sodium hydroxide; the virtual insolubility of sodium dibenzyl phosphate in excess of sodium hydroxide solution greatly facilitates isolation of the product.

It is of interest that the system dibenzyl phosphite–carbon tetrachloride–aqueous caustic alkali can give either tetrabenzyl pyrophosphate (when N-potassium hydroxide is used) or sodium dibenzyl phosphate (when 10N-sodium hydroxide is used).

Experimental.

Action of Various Bases on Tribenzyl Phosphate (Experiments at 100° for 2 Hours).—All the bases were freshly distilled over solid potassium hydroxide, and in each experiment 1 g. of tribenzyl phosphate and 10 c.c. of anhydrous base were employed. All reaction mixtures were worked up in the same manner. A typical example follows:

A solution of tribenzyl phosphate (1 g.) in freshly distilled 4-methylmorpholine (10 c.c.) was heated at 100° for 2 hours. Excess of base was removed under reduced pressure and the residual gum shaken with a mixture of aqueous sodium hydroxide (20 c.c. of 5%) and ether (30 c.c.). The alkaline aqueous layer was separated, washed with a further quantity of ether (30 c.c.), acidified with sulphuric acid (20 c.c. of 3N), and rapidly extracted with chloroform (2 × 75 c.c.). (The acidification always produces an opalescence if debenzylation has proceeded to any considerable extent.) The chloroform extracts were combined, washed twice with water, dried (Na_2SO_4), and evaporated under reduced pressure. The

residual oil crystallised on addition of ether; the product (0·49 g., 65%) had m. p. 77°, undepressed on admixture with an authentic specimen of dibenzyl hydrogen phosphate (m. p. 78°).

The ethereal extract and washings of the original alkaline solution were combined, washed with hydrochloric acid (2 × 20 c.c. of 3N.), then with water (2 × 25 c.c.), and dried (Na_2SO_4). Evaporation gave a colourless oil (0·103 g.) which when rubbed set to a mass of crystals, m. p. 61°, undepressed on admixture with an authentic specimen of tribenzyl phosphate (m. p. 63—64°); hence recovery of starting material = 10%.

From a series of experiments similar to that outlined above but using morpholine, pyridine, 2-picoline, 2 : 6-lutidine, quinoline, and quinaldine as the base the results quoted in the Introduction were obtained. It is of interest to note that, if 10% sodium hydroxide solution is used in place of the 5% solution indicated in the isolation procedure, three layers are formed and sodium dibenzyl phosphate may crystallise out and so interfere with the separation and the determination of the yield.

Three experiments were carried out at the boiling points of the bases concerned, *viz.*, with 4-methylmorpholine (116°), pyridine (115°), and with triethylamine (89°). The yields of dibenzyl hydrogen phosphate were 87%, 61%, and 26% respectively. In the experiment using triethylamine, recovery of crystalline tribenzyl phosphate amounted to 58%.

Several experiments were carried out in pyridine solution to determine the speed of debenzylation at 100°. After a pyridine solution of tribenzyl phosphate had been heated at 100° for 15 minutes, the yield of dibenzyl hydrogen phosphate amounted to 55%, together with a recovery of 39% of tribenzyl phosphate. After 1 hour at 100°, the yield was 85% and the recovery 4%, and after 2 hours at 100° the yield was 62%, the recovery being 2%.

Comparison of 2- and 4-Picoline in Their Reaction with Tribenzyl Phosphate.—These reactions were carried out by using 1 g. of the substrate in 10 c.c. of the anhydrous base. Heating was at 100° for 1 hour and the reaction mixture worked up as described above. In the case of 2-picoline, the yield of dibenzyl hydrogen phosphate was 9% and the recovery of unchanged tribenzyl phosphate 72%. The corresponding figures for 4-picoline were 74% and 15%.

Reactions with Aniline and Its Methyl Derivatives.—These reactions were carried out at 100° for 2 hours and the reaction mixtures worked up as before. With aniline a 79% yield of crystalline dibenzyl hydrogen phosphate was obtained, and with methylaniline a 75% yield. In each case the amount of tribenzyl phosphate recovered was negligible. With dimethylaniline the debenzylated product was obtained in 15% yield only and did not crystallise, whereas 65% of the starting material was recovered crystalline.

Action of Bases on Dibenzyl Hydrogen Phosphate.—(a) *Pyridine.* Dibenzyl hydrogen phosphate (10 g.) was dissolved in anhydrous pyridine (75 c.c.), and the solution refluxed for 6 hours, moisture being excluded throughout. Excess of pyridine was removed under reduced pressure in a stream of dry air, and the residual oil was dissolved in water (30 c.c.). The solution was acidified with sulphuric acid (30 c.c. of 3N.) and extracted with chloroform (3 × 50 c.c.). The chloroform extract was washed twice with water, dried (Na_2SO_4), and evaporated at atmospheric pressure to leave a colourless oil which solidified when seeded with dibenzyl hydrogen phosphate (4·41 g., 44% recovery).

The aqueous acidic residue remaining after chloroform extraction was neutralised with excess of barium carbonate and left overnight. The solid was filtered off and then boiled with excess of dilute sulphuric acid for 30 minutes. The acid solution so obtained was freed from barium sulphate, and the total inorganic phosphate in the filtrate determined as phosphomolybdate. The weight of phosphorus so determined was 245 mg., *i.e.*, at least 22% of the phosphorus originally present in the dibenzyl hydrogen phosphate was liberated as inorganic phosphate.

(b) *Dimethylaniline.* Dibenzyl hydrogen phosphate (4·0 g.) was dissolved in freshly distilled dimethylaniline (30 c.c.), and the solution divided into two equal portions. One was worked up immediately to provide a check on the procedure, while the other was heated at 100° for 2 hours before being worked up by the following method.

The reaction mixture was diluted with ether (50 c.c.) and the whole extracted with aqueous sodium hydroxide (2 × 30 c.c. of 5%). The alkaline extracts were combined and acidified with sulphuric acid (40 c.c. of 3N.). The opalescent acid solution was now extracted with chloroform (3 × 100 c.c.), and the chloroform extract washed with water, dried (Na_2SO_4), and evaporated yielding dibenzyl hydrogen phosphate. Recovery in the case where isolation of the acid was carried out immediately after dissolution in the base was 1·924 g. (96%). This was converted into its *cyclo*hexylamine salt (Part V of this series, *loc. cit.*) which was obtained in a yield of 90% based on the weight of acid originally dissolved in the base.

In the case where the dimethylaniline solution of dibenzyl hydrogen phosphate had been heated to 100° for 2 hours, the recovery (as *cyclo*hexylamine salt) was 1·905 g. (70%). Extension of the period of heating to 6 hours caused the amount of material recovered to fall to 58%.

Effect of Pyridine Hydrochloride on the Reaction between Pyridine and Tribenzyl Phosphate.—Tribenzyl phosphate (1 g., 1 mol.) and freshly prepared pyridine hydrochloride (315 mg., 1 mol.), dissolved in freshly distilled pyridine (10 c.c.), were heated at 100° for 2 hours. The base was then removed under reduced pressure and the residue worked up as described above for the reaction of tribenzyl phosphate with 4-methylmorpholine. The yield of dibenzyl hydrogen phosphate was 0·46 g. (61%). The neutral fraction, usually tribenzyl phosphate, was an oil smelling of benzyl chloride. This oil was repeatedly evaporated with water until no longer lachrymatory. The residue weighed 40 mg. (4%).

Effect of 2 : 6-Lutidine Hydrochloride on the Reaction between 2 : 6-Lutidine and Tribenzyl Phosphate.—2 : 6-Lutidine hydrochloride is sparingly soluble in 2 : 6-lutidine, but is soluble in hot ethoxyethanol.

Ethoxyethanol was therefore used as diluent and solvent. A blank experiment using tribenzyl phosphate (1 g.) in a mixture of ethoxyethanol (10 c.c.) and 2 : 6-lutidine (10 c.c.) showed that the ethoxyethanol had no apparent effect on the base–phosphate ester reaction.

Tribenzyl phosphate (1 g., 1 mol.) and 2 : 6-lutidine hydrochloride (390 mg., 1 mol.), dissolved in a mixture of 2 : 6-lutidine (10 c.c.) and ethoxyethanol (10 c.c.), were heated at 100° for 2 hours. Excess of base and of diluent was then removed under reduced pressure, and the residue worked up in the usual manner. The yield of dibenzyl hydrogen phosphate obtained was 0·23 g. (31%). The recovered material, an oil, was a potent lachrymator, but, on its evaporation with water, the lachrymatory material (benzyl chloride) was removed and the residue then crystallised (0·46 g., 46%), having m. p. 61°, undepressed on admixture with an authentic specimen of tribenzyl phosphate.

Action of Base Hydrochlorides on Tribenzyl Phosphate.—(a) *Pyridine hydrochloride.* Pyridine hydrochloride (530 mg., 1 mol.) and tribenzyl phosphate (1·70 g., 1 mol.), dissolved in ethoxyethanol (25 c.c.), were heated at 100° for 2 hours, moisture being excluded by a silica-gel tube. The resulting solution was worked up in the usual manner, yielding dibenzyl hydrogen phosphate (0·67 g., 52%); tribenzyl phosphate (0·54 g., 32%) was recovered.

(b) 2 : 6-*Lutidine hydrochloride.* With 2 : 6-lutidine hydrochloride in place of pyridine hydrochloride in the above experiment, the yield of dibenzyl hydrogen phosphate was 55% and the recovery of tribenzyl phosphate 28%.

Sodium Dibenzyl Phosphate.—Crude dibenzyl phosphite (52 g., purity 71%) was dissolved in carbon tetrachloride (250 c.c.) and the solution cooled in ice. A solution of sodium hydroxide (80 g.) in water (160 c.c.) was added slowly with vigorous stirring during 30 minutes. Heat was evolved and a copious white precipitate of sodium dibenzyl phosphate formed almost immediately. Stirring was continued for 5 hours at room temperature and the reaction was then completed by refluxing the mixture on the water-bath with stirring for 2 hours to convert any tetrabenzyl pyrophosphate present into sodium dibenzyl phosphate. The mixture was cooled and the crude sodium salt collected. The salt was washed with carbon tetrachloride, then with dilute sodium hydroxide solution, and finally dried at room temperature *in vacuo* over phosphoric oxide. The salt so obtained was the stable *tetrahydrate* (46·5 g., 88%) (Found: C, 44·9; H, 5·7; loss at 140°/0·2 mm., 19·5. $C_{14}H_{14}O_4PNa,4H_2O$ requires C, 45·1; H, 6·9; H_2O, 19·3%). It can be recrystallised from chloroform from which it separates as colourless plates, m. p. 63°, resolidifying between 70° and 80° as a monohydrate. The tetrahydrate shows an interesting behaviour with ethyl acetate. It is immediately soluble in the cold ester but is rapidly redeposited, the product now melting at 295° (decomp.); presumably the salt is dehydrated by the solvent.

Conversion of Crude Sodium Dibenzyl Phosphate into Silver Dibenzyl Phosphate.—The crude sodium salt (100 g.) was dissolved in water (1750 c.c.) with gentle heating. The solution was cooled and brought to neutrality by the addition of dilute nitric acid (phenolphthalein). To this solution was added, slowly with stirring, a solution of silver nitrate (63·0 g.) in water (600 c.c.), the system being protected from light as much as possible. White crystals of silver dibenzyl phosphate separated immediately. After the addition was complete, the product was filtered off, washed well with distilled water, and dried *in vacuo* over phosphoric oxide. The yield was 85 g.

Grateful acknowledgment is made to the Department of Scientific and Industrial Research for a Maintenance Allowance, to Gonville and Caius College for the award of the Dunlop Studentship, and to the University of Cambridge for the award of the W. A. Meek Scholarship (to V. M. C.).

University Chemical Laboratory, Cambridge. [*Received, May 1st,* 1950.]

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416. *Studies on Phosphorylation. Part VII. The Action of Salts on Neutral Benzyl Esters of the Oxy-acids of Phosphorus. A New Method of Selective Debenzylation.*

By V. M. Clark and A. R. Todd.

The observation that monodebenzylation of tribenzyl phosphate can be accomplished by reaction with a base hydrochloride (Clark and Todd, preceding paper) has been extended to include reaction with a quaternary ammonium salt and with a variety of inorganic salts. Benzyl esters of various phosphorous, phosphoric, and aminophosphonic acids have been shown to undergo the reaction with ease. In the majority of cases an ethoxyethanol solution of lithium chloride is most effective and this reagent is recommended for use in monodebenzylation.

The investigations described in this series of papers have had as their primary objective the development of phosphorylation methods which, while mild enough in operation to be applied to sensitive molecules, would at the same time be sufficiently flexible to permit their extension to the production of pyro- and poly-phosphoric esters. For many purposes the reagent of choice has been dibenzyl chlorophosphonate (Atherton, Openshaw, and Todd, *J.*, 1945, 382) and this has proved to be of great value in the nucleotide field (cf. *J.*, 1947, 648; 1949, 582, 2476, 2487) because of the ease with which the benzyl groups may be removed from the initial

products of reaction and because it is possible in various ways to remove one benzyl group selectively, thereby providing suitable starting materials for polyphosphate synthesis. One method of selective monodebenzylation which can be applied to neutral benzyl esters of phosphorous, phosphoric, and pyrophosphoric acids is the reaction with a tertiary base (Baddiley, Clark, Michalski, and Todd, *J.*, 1949, 815). Studies on the range of applicability of this reaction with respect to the nature of both the base and the substrate ester have led to a correlation of certain aspects of the chemistry of the oxy-acids of phosphorus and sulphur and to a general interpretation of the reaction (Clark and Todd, Part VI, preceding paper). A further outcome of these studies was the demonstration that monodebenzylation could also be brought about by the action of base hydrochlorides, and, following up this observation, we investigated the action of a quaternary ammonium salt. 4-Benzyl-4-methylmorpholinium chloride and tribenzyl phosphate at 100° for 2 hours in ethoxyethanol gave a moderate yield of dibenzyl hydrogen phosphate. It was then clear that debenzylation was occurring in accordance with a mechanism of the type :

$$Cl^- \longrightarrow Ph{\cdot}CH_2{\cdot}O{\cdot}PO(O{\cdot}CH_2Ph)_2 \longrightarrow Ph{\cdot}CH_2Cl + {}^-O{\cdot}PO(O{\cdot}CH_2Ph)_2$$

This is, of course, the type A mechanism of Clark and Todd (*loc. cit.*) in which, as previously suggested, the anion causing debenzylation can be supplied from an external source. The present communication deals with the extension of the reaction to anions in general and the development of a very convenient practical procedure for monodebenzylation.

When tribenzyl phosphate was heated with three molecular proportions of lithium chloride in ethoxyethanol at 100°, lithium dibenzyl phosphate crystallised from the reaction mixture and after 2 hours the yield was almost quantitative. This simple monodebenzylation method seems to be generally applicable to neutral phosphorous and phosphoric esters containing benzyl groups. Under the same conditions dibenzyl phosphite gave the crystalline lithium monobenzyl phosphite which was very sparingly soluble in ethoxyethanol and began to separate after a few minutes' heating. Phenyl dibenzyl phosphate and 2-hydroxy*cyclo*hexyl dibenzyl phosphate were similarly converted in excellent yield into the corresponding monobenzyl esters (isolated as *cyclo*hexylamine salts).

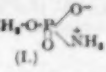
This process of anionic debenzylation using metallic salts is confined neither to lithium salts nor to chlorides. Potassium acetate was almost as effective as lithium chloride in converting tribenzyl phosphate into dibenzyl hydrogen phosphate although in this case no crystalline salt separated during the reaction. Lithium acetate, on the other hand, was less effective owing to its low solubility, when anhydrous, in the preferred reaction media (ethanol or ethoxyethanol). Lithium nitrate was much less effective than lithium chloride, and gave dibenzyl hydrogen phosphate in 38% yield under conditions where the latter gave 80—90%. These findings suggest that we are dealing here with an equilibrium reaction, the results obtained depending *inter alia* on the position of equilibrium, the rate of attainment of that position, and the relative solubilities of the various salts present :

$$X^- + Ph{\cdot}CH_2{\cdot}O{\cdot}PO(OR)_2 \rightleftharpoons Ph{\cdot}CH_2X + (RO)_2PO{\cdot}O^-$$

If all components remain in solution the position of equilibrium will be in favour of debenzylation if the attacking anion is less " stable " in solution than the substituted phosphate anion, *i.e.*, if it is the anion of a weaker acid. In other words, the stronger an acid the less effective will be its anion in the debenzylating reaction. This is well illustrated in the series trifluoroacetate, nitrate, acetate; under comparable conditions (2 hours at 100° in ethoxyethanol) the yields of dibenzyl hydrogen phosphate from tribenzyl phosphate with these anions were 23%, 38%, and 75% respectively. It must be borne in mind, however, that these considerations apply only when all components are in solution; they do not apply in the case of lithium chloride, for example, since lithium dibenzyl phosphate crystallises from the reaction solution thereby displacing the equilibrium in the direction of debenzylation. Lithium salts of substituted phosphoric acids are frequently rather sparingly soluble in ethoxyethanol so that, from a practical standpoint, lithium chloride in ethoxyethanol is usually the preferred reagent for the monodebenzylation of phosphates. This tendency of lithium salts to separate can also be turned to advantage in the monodebenzylation of dibenzyl esters of aminophosphonic acids.

Attention was drawn in earlier papers (*locc. cit.*) to the difficulty of debenzylating aminophosphonates and to our inability to bring about reaction between dibenzyl aminophosphonate and tertiary bases. On heating dibenzyl aminophosphonate with lithium chloride in ethoxyethanol under the conditions used for monodebenzylating tribenzyl phosphate, only a small

quantity of a lithium salt separated and the high water-solubility of the debenzylated product made its isolation from the reaction solution very difficult. When however a saturated solution of lithium chloride in ethoxyethanol was used as the debenzylating reagent, the high concentration of chloride displaced the equilibrium in the desired direction while the high lithium ion concentration facilitated precipitation of the desired lithium benzyl aminophosphonate. With this method the yield of precipitated lithium salt was 57% after 2 hours, rising to a maximum of 78% after 6 hours (reaction temperature 100°); the variation of yield with time supports the contention that an equilibrium reaction is involved. It is of interest that the precipitated lithium benzyl aminophosphonate in these experiments was completely free from chloride ion. The free benzyl aminophosphonic acid prepared from the lithium salt formed a crystalline hemihydrate. The anhydrous acid has m. p. *ca.* 200° which suggests that it exists as the zwitterion (I). It will be seen that (I) is in fact a "base–metaphosphate complex" (cf. Langheld, *Ber.*, 1911, **44**, 2076) and when heated it loses ammonia yielding, presumably, benzyl metaphosphate. Under the conditions employed for dibenzyl aminophosphonate, dibenzyl anilinophosphonate was also monodebenzylated in good yield; lithium benzyl anilinophosphonate separated from the reaction mixture and the free acid was characterised as its *cyclo*hexylamine salt.



(I.)

An interesting effect has been observed when using a combination of the tertiary base and anionic debenzylation methods. It was reported in Part VI (preceding paper) that 2-picoline, for steric reasons, is an ineffective debenzylating agent for tribenzyl phosphate and, as pointed out above, the trifluoroacetate anion likewise has but little effect. However, a mixture of 2-picoline and potassium trifluoroacetate, dissolved in ethoxyethanol, is quite an effective debenzylating system; this is probably to be attributed to a displacement of the anionic equilibrium by interaction of the tertiary base with the benzyl trifluoroacetate formed.

In all the examples of lithium chloride debenzylation we have studied, an increase in the temperature of reaction has led to an increase in yield; this will not necessarily be true in all cases, of course, since although an increase in temperature will always increase the rate of attainment of equilibrium its effect on the position of equilibrium may vary. The anionic fission of esters of the phosphorus oxy-acids here described applies generally to the removal of benzyl or substituted benzyl groups. Triphenyl phosphate as might be expected is unaffected by lithium chloride, but the successful application of the method to dibenzyl esters of aminophosphonic acids makes it not improbable that, under appropriate conditions, secondary or even primary alkyl groups may be removed by anionic fission; this is under investigation. Should anionic dealkylation prove to be possible in aqueous solution the method might have some application in the degradation of polynucleotides. It will be observed that all the reactions described in this paper have been formulated as bimolecular displacements. A unimolecular solvolytic mechanism may also play a part, however, since a transient yellow colour has been observed in certain cases and Roberts and Hammett (*J. Amer. Chem. Soc.*, 1937, **59**, 1063) have pointed out that the benzyl cation is probably yellow. Although the part played by the unimolecular mechanism would be very small in the examples here reported, it would doubtless become more important in solvents of higher dielectric strength—conditions which would affect the bimolecular mechanism adversely; for this reason the overall effect of water on the debenzylation process cannot be accurately predicted.

Experimental.

Action of Various Salts on Tribenzyl Phosphate.—(a) *4-Benzyl-4-methylmorpholinium chloride.* The quaternary salt (910 mg., 1 mol.) and tribenzyl phosphate (1·46 g., 1 mol.) were dissolved in freshly distilled ethoxyethanol (25 c.c.) and the solution was heated at 100° for 2 hours. Solvent was removed under reduced pressure and the oily residue which smelt strongly of benzyl chloride was worked up for dibenzyl hydrogen phosphate in the usual manner. The yield was 0·48 g. (44%). 0·7 g. (48%) of unchanged tribenzyl phosphate being recovered.

(b) *Lithium chloride.* Anhydrous (fused) lithium chloride (1·38 g., 3 mols.), and tribenzyl phosphate (3·68 g., 1 mol.) were dissolved in freshly distilled ethoxyethanol (25 c.c.) and the solution heated at 100° for 2 hours. During the reaction colourless needles of *lithium dibenzyl phosphate* separated and benzyl chloride was formed. Aqueous sodium hydroxide (40 c.c. of 5%) was added to the cooled mixture and the whole extracted with ether (2 × 50 c.c.). The alkaline layer was acidified with sulphuric acid, so precipitating a colourless oil which quickly solidified. This was taken up in chloroform and the solution dried (Na_2SO_4), filtered, and evaporated, to leave a crystalline mass of dibenzyl hydrogen phosphate (2·74 g.; almost quantitative). Recrystallised from chloroform–light petroleum it formed colourless needles (2·24 g., 80%), m. p. 78—79° alone or mixed with an authentic specimen. In a second experiment the crystalline lithium dibenzyl phosphate was filtered off directly from the reaction mixture

and recrystallised from aqueous acetone, forming colourless needles, m. p. 292—293° (decomp.) (Found: C, 59·0; H, 5·1. $C_{14}H_{14}O_4PLi$ requires C, 59·1; H, 5·0%). When ethanol was used as a solvent and the reaction carried out by refluxing the solution for 4½ hours the yield of dibenzyl hydrogen phosphate was only 38%.

(c) *Lithium acetate.* Lithium acetate dihydrate was fairly readily soluble in ethanol, but the anhydrous salt was much less so and was very sparingly soluble in ethoxyethanol. On heating an ethoxyethanol solution of the dihydrate above 40° the salt—presumably in anhydrous form—separated from solution. When the dihydrate (3 mols.) was heated under reflux in ethanol with tribenzyl phosphate (1 mol.) for 2 hours and worked up as in the lithium chloride experiment the yield of dibenzyl hydrogen phosphate was 13%, a large amount (61%) of tribenzyl phosphate being recovered unchanged.

(d) *Potassium acetate.* After a solution of tribenzyl phosphate in ethoxyethanol (0·4M.; 1 mol.) had been heated with anhydrous potassium acetate (3 mols.) at 100° for 2 hours, no crystalline material separated but by working up as described above dibenzyl hydrogen phosphate (75%) was obtained.

(e) *Lithium nitrate.* Under the same conditions (3 mols. of salt and 1 mol. of ester in ethoxyethanol at 100° for 2 hours) the yield of dibenzyl hydrogen phosphate was 38%.

(f) *Potassium trifluoroacetate.* Under the same conditions in ethoxyethanol at 100° potassium trifluoroacetate and tribenzyl phosphate gave after 2 hours dibenzyl hydrogen phosphate in 23% yield, together with 69% of unchanged ester.

Phenyl Benzyl Hydrogen Phosphate.—Phenyl dibenzyl phosphate (1·59 g., 1 mol.) (Baddiley, Clark, Michalski, and Todd, *loc. cit.*) and anhydrous lithium chloride (580 mg., 3 mols.) were heated in ethoxyethanol (20 c.c.) for 3 hours at 100°. No crystalline salt separated but the mixture smelt strongly of benzyl chloride. When the products were worked up for dibenzyl hydrogen phosphate as described above, phenyl benzyl hydrogen phosphate (1·054 g., 89%) was obtained as a viscous syrup. This syrup was dissolved in ether (30 c.c.), and ethereal *cyclo*hexylamine (685 mg. in 15 c.c.) added. The *cyclo*hexylamine salt separated rapidly. More ether (20 c.c.) was added and after 5 minutes the salt (1·05 g., 65%) was collected, dried at 80°, and recrystallised from ethanol–acetone. It formed long silky needles, m. p. 147°, undepressed on admixture with an authentic specimen (m. p. 147°; Part V, *loc. cit.*).

2-Hydroxycyclohexyl Benzyl Hydrogen Phosphate.—2-Hydroxy*cyclo*hexyl dibenzyl phosphate (1·24 g., 1 mol.) (Baddiley, Clark, Michalski, and Todd, *loc. cit.*) and anhydrous lithium chloride (570 mg., 3 mols.) were heated in ethoxyethanol (25 c.c.) at 100° for 2 hours. The mixture worked up as before yielded the water-soluble 2-hydroxy*cyclo*hexyl benzyl hydrogen phosphate as a colourless oil (823 mg., 88%). The free acid was characterised by dissolution in ether and conversion into its *cyclohexylamine* salt in the usual manner. Recrystallised from ethanol the salt formed colourless needles, m. p. 179° (Found: C, 59·2; H, 8·2; N, 3·7. $C_{19}H_{32}O_4NP$ requires C, 59·2; H, 8·4; N, 3·6%).

Lithium Monobenzyl Phosphite.—A hot solution of dibenzyl phosphite (5·48 g., 1 mol.) in ethoxyethanol (10 c.c.) was added to a solution of anhydrous lithium chloride (1·7 g., 2 mols.) in ethoxyethanol (15 c.c.) at 100°. A crystalline precipitate began to form within 1 minute of mixing. The mixture was kept at 100° for 2 hours and the precipitated ***lithium monobenzyl phosphite*** (2·79 g., 76%) then collected, washed with hot solvent, and dried at 100°. The salt obtained in this way was a fine white powder, m. p. >350°; although hydrophobic in this condition it was in fact appreciably soluble in water but sparingly so in ethanol. Recrystallised from aqueous ethanol, it formed colourless nacreous plates (Found: C, 47·4; H, 4·9. $C_7H_8O_4PLi$ requires C, 47·2; H, 4·6%). The lithium salt was converted into the ammonium salt by acidification, extraction of the free acid with chloroform, and saturation of the concentrated extract with ammonia; recrystallised from ethoxyethanol–dioxan it formed colourless needles, m. p. 154°, undepressed on admixture with an authentic specimen (Part V, *loc. cit.*).

Prolongation of the period of heating with lithium chloride to 4½ hours gave no increase in yield. In a series of similar experiments in ethanolic solution at 78° the yields of lithium monobenzyl phosphite were: after 1 hour, 48%; after 2 hours, 54%; after 4½ hours, 65%. In all cases the amount of monobenzyl phosphite which could be obtained by working up the mother-liquor after filtration of the lithium salt was negligible.

Monobenzyl Hydrogen Aminophosphonate.—Selective debenzylation of dibenzyl aminophosphonate was best carried out by using a hot saturated solution of lithium chloride in ethoxyethanol (solubility 16·4 g. per 100 g. of solution at 100°).

Dibenzyl aminophosphonate (5·19 g.) was heated for 10 hours with a saturated solution of anhydrous lithium chloride in ethoxyethanol at 100° (25 c.c.). After 15 minutes the mixture became opalescent and a solid began to separate. The amount of *lithium monobenzyl aminophosphonate* which had separated was estimated by collection on a sintered-glass funnel at various intervals; after 3 hours it weighed 2·42 g. (67%), and after 6 hours 2·82 g. (78%), no further deposition occurring thereafter. A second experiment under the same conditions gave a yield of 57% in 2 hours and 72% in 4 hours. The lithium salt separated from water as colourless needles having no definite m. p. Placed in a bath at 265° and further heated it shrank at 282°, then gradually became translucent, and finally transparent over the range 295—310° (Found: C, 43·3; H, 4·7; N, 7·0. $C_7H_9O_3NPLi$ requires C, 43·5; H, 4·7; N, 7·3%).

When the above lithium salt (1·4 g.) was dissolved in warm water (15 c.c.), acidified with dilute sulphuric acid (7 c.c. of 3N.), and set aside at 0° ***monobenzyl hydrogen aminophosphonate*** separated as colourless plates, apparently of a hemihydrate (Found: C, 43·1; H, 5·7; N, 7·2. $C_7H_{10}O_3NP,\frac{1}{2}H_2O$ requires C, 42·9; H, 5·7; N, 7·2%). When heated, the hemihydrate showed an indefinite m. p., shrinking at 102° and becoming translucent at 106°. If placed in a bath at 180°, however, it melted immediately, then resolidified, and if heated quickly above this temperature melted at 199—200° without apparent decomposition. This somewhat anomalous behaviour is doubtless due to the fact that the

acid gradually loses ammonia on heating, thereby precluding its preparation in anhydrous form from the hemihydrate by the usual methods of drying.

Monobenzyl Hydrogen Anilinophosphonate.—Dibenzyl anilinophosphonate (2·86 g.) was dissolved in ethoxyethanol (25 c.c.) saturated with lithium chloride at 100° and the mixture was heated for 1½ hours at 100°. After 30 minutes solid began to separate and a marked odour of benzyl chloride was apparent. Water (20 c.c.) and ether (50 c.c.) were added to the cooled mixture which was then filtered. Aqueous sodium hydroxide (15 c.c. of 10%) was added to the filtrate and the layers were separated. The aqueous alkaline layer was again extracted with ether (2 × 50 c.c.), the filtered solid added to the aqueous phase, and the mixture acidified with dilute sulphuric acid (30 c.c. of 3N.). The opalescent solution was extracted with ethyl acetate (3 × 100 c.c.), and the combined extracts were washed with water, dried (Na_2SO_4), and evaporated under reduced pressure (bath-temp. 40°/0·2 mm.), yielding *monobenzyl hydrogen anilinophosphonate* (1·77 g., 83%) as a pale yellow amorphous solid (Found: C, 58·5; H, 5·3. $C_{13}H_{14}O_3NP$ requires C, 59·3; H, 5·4%), which resinified on attempting to recrystallise it from benzene. It was, therefore, dissolved in ethyl acetate and converted into its *cyclohexylamine* salt which crystallised from acetone containing a few drops of ethanol, as colourless plates, m. p. 180—181° (Found: C, 62·8; H, 7·8; N, 7·7. $C_{19}H_{27}O_3N_2P$ requires C, 63·0; H, 7·5; N, 7·7%).

Action of a Mixture of Potassium Trifluoroacetate and 2-Picoline on Tribenzyl Phosphate.—Tribenzyl phosphate (1·09 g.) and potassium trifluoroacetate (1·25 g.), dissolved in a mixture of 2-picoline (5 c.c.) and ethoxyethanol (5 c.c.), were heated for 1 hour at 100°. A transient yellow colour appeared, which faded on cooling and reappeared on heating. After 1 hour the mixture was worked up in the usual manner to give dibenzyl hydrogen phosphate (0·4 g., 49%), together with unchanged tribenzyl phosphate (0·36 g., 33%).

Under the same conditions, but with 2-picoline alone, the yield of dibenzyl hydrogen phosphate was only 19%, and, when potassium trifluoroacetate was used alone, the 2-picoline being replaced by an additional 5 c.c. of ethoxyethanol, the yield was 15%. Potassium trifluoroacetate had no beneficial effect on the action of 2 : 6-lutidine as a debenzylating agent for tribenzyl phosphate, some 91% of which was recovered unchanged after 1 hour in ethoxyethanol at 100°. A mixture of pyridine and potassium trifluoroacetate, on the other hand, gave a 93% yield of crystalline dibenzyl hydrogen phosphate under analogous conditions.

Grateful acknowledgment is made to the Department of Scientific and Industrial Research for a Maintenance Allowance, to Gonville and Caius College for the award of the Dunlop Studentship, and to the University of Cambridge for the award of the W. A. Meek Scholarship (to V. M. C.).

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417. *Acylation Reactions catalysed by Strong Acids. Part II. "Acetyl Perchlorate" as a C-Acetylating Agent.*

By H. BURTON and P. F. G. PRAILL.

"Acetyl perchlorate," prepared *in situ* from silver perchlorate and acetyl chloride, is an effective acetylating agent and will convert anisole, in the absence of added solvent, into *p*-methoxyacetophenone in approximately 70% yield. The effect of adding acetic acid or acetic anhydride or both to the reaction mixture is studied in detail. The results support the view that Ac^+ and Ac_2OH^+ are both acetylating agents, the former being much the more reactive. The dehydration of the ion $AcOH_2^+$ is discussed briefly.

In Part I (J., 1950, 1203) we showed that solutions of concentrated aqueous perchloric acid in an excess of acetic anhydride contain acetylium (Ac^+) and probably acetic anhydridium (Ac_2OH^+) ions, or both, because of the occurrence of the reactions

$$H^+ + Ac_2O \rightleftharpoons Ac_2OH^+ \rightleftharpoons Ac^+ + AcOH \quad . \quad . \quad . \quad . \quad . \quad . \quad (1a)$$

or

$$AcOH_2^+ + Ac_2O \rightleftharpoons Ac_2OH^+ + AcOH \rightleftharpoons Ac^+ + 2AcOH \quad . \quad . \quad . \quad . \quad (1b)$$

We were unable to prove conclusively whether the acetylium ion was the sole reactive species for acetylation: in fact, some qualitative evidence was advanced to support the view that both ions are active agents but that acetylium was more reactive than acetic anhydridium. In order to attempt to clarify this point we decided to investigate the use of "acetyl perchlorate" as a *C*-acetylating agent. It has been shown by Mackenzie and Winter (*Trans. Faraday Soc.*, 1948, **44**, 159, 171, 243) that "acetyl perchlorate" (acetylium perchlorate), $AcClO_4$, prepared from equimolecular amounts of silver perchlorate and acetyl chloride in acetic anhydride, is an effective catalyst for the Thiele acetylation reaction, and also for *O*-acetylation (Winter, private communication). Acetylium perchlorate was shown (*loc. cit.*) to be a "strong acid" in acetic anhydride solution, indicating the dissociation, $AcClO_4 \rightleftharpoons Ac^+ + ClO_4^-$. It was essential for our purpose to avoid, in the first place, the use of acetic anhydride since the subsequent addition

of any substance capable of being acetylated would result in the formation of hydrogen ions which would clearly then undergo reaction (1*a*).

Since anhydrous silver perchlorate is freely soluble in anisole we first investigated the reaction between acetylium perchlorate and the ether alone, by adding 1 mol. of acetyl chloride to a solution of 1 mol. of the silver salt in 4 mols. of anisole. After 45 minutes (or 2 hours) at 0—5° we were able (Expt. *A*) to isolate approximately 0·7 mol. of *p*-methoxyacetophenone and to recover approximately 2·9 mols. of unchanged anisole. This result would appear at first sight to be rather surprising since anisole has a low dielectric constant, and the acetylium perchlorate prepared *in situ* would consequently not be expected to be dissociated to any appreciable extent. The production of the relatively large amount of ketone would indicate however that acetylium perchlorate is largely ionised, *i.e.*, the ion pair ($Ac^+ClO_4^-$), as distinct from being dissociated into the two ions Ac^+ and ClO_4^-. We expected therefore that if the reaction was carried out under otherwise identical conditions but in presence of a suitable amount of nitromethane,* the increased dielectric constant of the mixture would lead to an increased yield of ketone, presumably because of the increased rate of reaction; we were able to isolate at least 0·84 mol. (Expt. *B*) of *p*-methoxyacetophenone.

The effect of adding acetic acid to the original reaction mixture appeared to be the logical sequence. The yield of *p*-methoxyacetophenone remained constant (0·68 ± 0·04 mol.) in the presence of up to and including 6 mols. of acetic acid per mol. of acetylium perchlorate but showed a small decrease to 0·54 mol. when 8 mols. were added. In no case was the yield materially altered by the addition of nitromethane in such a quantity as to give a reaction mixture of approximately the same dielectric constant in comparable experiments, although generally the yields in the presence of nitromethane did tend to be very slightly higher. We do not attach undue importance to this particular observation except to emphasise that in the absence of acetic acid, the increase in yield in the presence of nitromethane was beyond the limitations of our experimental procedure. We feel justified in concluding that the results indicate the probable occurrence of the equilibrium ($Ac^+ClO_4^-$) + AcOH $\rightleftharpoons$ ($Ac_2OH^+ClO_4^-$), and that this tends to lie to the right when a relatively large amount of acetic acid is present in the reaction mixture. Furthermore, it would thus appear that acetic anhydridium perchlorate is relatively stable but is not as active as acetylium perchlorate. We are forced to this conclusion because of the experimental results when using added nitromethane, since if acetylium ions had a separate existence in acetic acid–nitromethane solution, we can see no reason why, under these conditions, the yield of ketone should not have increased in the same way as in the absence of any acid.

When the reaction between acetylium perchlorate (1 mol.) and anisole (4 mols.) was carried out in the presence of acetic anhydride (3 mols.) under otherwise identical conditions (Expt. 1), we obtained, as expected, an entirely different result. The yield of *p*-methoxyacetophenone was increased from approximately 0·7 mol. to approximately 1·6 mols. and thus exceeded that stoicheiometrically possible on the acetylium perchlorate used. This result proves conclusively that the reaction, PhOMe + Ac^+ ⟶ $OMe{\cdot}C_6H_4{\cdot}COMe + H^+$, is followed by reaction (1*a*) (above). The yield of ketone was unaltered by addition of 2 mols. of acetic acid (Expt. 2), but in this series of experiments we found that addition of nitromethane caused, in this particular case (Expt. 4), a marked increase in the yield of ketone to approximately 1·9 mols., thus indicating quite clearly that if the reaction, Ac^+ + AcOH ⟶ Ac_2OH^+, does occur to any appreciable extent then the acetic anhydridium ion is also capable of converting anisole into *p*-methoxyacetophenone. The reaction Ac_2OH^+ + PhOMe ⟶ $OMe{\cdot}C_6H_4{\cdot}COMe + AcOH_2^+$, would thus be followed by reaction (1*b*) (above).

Increasing the amount of acetic acid to 12 mols. (Expts. 5—7, 9, 10) resulted in the steady diminution in the yield of ketone to approximately 0·8 mol., thus affording a clear indication that acetylium ions do react with acetic acid to give the much less reactive, but nevertheless still active, acetic anhydridium ions. We should point out, however, that in these experiments the dielectric constant of the reaction mixture was steadily reduced by the increasing amount of acetic acid, and we fully expected that since acetic anhydride was present in this series of experiments as distinct from our first series, the yield of ketone would be influenced by added nitromethane. Comparison of Expts. 7 and 8 (as well as 2 and 4) shows quite clearly that such is the case: the yield of ketone being increased by at least 25%.

An alternative explanation is that the equilibria in reactions (1*a*) and (1*b*) lie well to the right and that the effect of added acetic acid is to *inactivate* some of the acetylium ions as acetic

* We have also used methyl cyanide as a diluent with very similar results: nitromethane is however a much more satisfactory solvent.

anhydridium ions. The result of adding nitromethane would thus be to favour the dissociation, $Ac_2OH^+ \longrightarrow Ac^+ + AcOH$. We suggest however that the results in acetic acid alone do not support this alternative explanation.

Except where stated otherwise 0·05 g.-mol. of silver perchlorate was dissolved in anisole (0·2 g.-mol.), and acetic anhydride (0·15 g.-mol.), acetic acid (amount in g.-mol. given in column 2), and acetyl chloride (0·05 g.-mol.) added dropwise with shaking. All the experiments were carried out at 0—5°, and the mixture was kept for 45 minutes. In the experiments (*B*, 4, 8) carried out with nitromethane as solvent the amount used was always twice the combined weights of anisole, acetic anhydride, and acetic acid. Expts. *A* and *B*, included for comparison, are those in which *neither* acetic acid *nor* acetic anhydride was present.

Expt.	AcOH present, g.-mol.	MeO·C_6H_4·COMe isolated, g.-mol.	PhOMe recovered, g.-mol.	Residue from distillation,* g.	Remarks.
A.	0	0·034	0·144	0·3	
B.	0	0·042	—	0·2	$MeNO_2$ added.
1.	0	0·079	0·09	1·0	
2.	0·1	0·08	0·1	0·2	
3.	0·1	0·073	0·1	0·1	PhOMe added last.
4.	0·1	0·093	—	0·4	$MeNO_2$ added.
5.	0·2	0·089	0·1	0·4	
6.	0·3	0·059	0·12	0·3	
7.	0·4	0·051	0·12	0·1	
8.	0·4	0·063	—	0·4	$MeNO_2$ added.
9.	0·5	0·048	0·13	0·2	
10.	0·6	0·039	0·133	0·3	

* The residue consists largely of *p*-methoxyacetophenone which was identified as the 2 : 4-dinitrophenylhydrazone.

In Part I (*loc. cit.*) we did not study the effect of added nitromethane on the activity of the acetic anhydride–aqueous perchloric acid mixtures. We now show that, in accordance with expectation, the yield of *p*-methoxyacetophenone obtained from anisole is increased to much the same extent as in the experiments using acetylium perchlorate. We have also compared mixtures of the same composition prepared with either 72% perchloric acid or acetyl chloride–silver perchlorate, the only difference being that the latter mixture contains suspended silver chloride, and we find as expected, that the amount of acetylation is the same irrespective of the method of preparation. In these experiments, we had necessarily—for reasons discussed fully in Part I—to add the anisole to the solution containing acetylium. We first investigated (Expt. 3) the effect of this mode of addition: the yield of ketone was not quite as good as in Expts. 1 and 2 but showed clearly the increase over the stoicheiometric amount.

We wish to emphasise that the yields of *p*-methoxyacetophenone quoted throughout this paper and Part I (*loc. cit.*) were those actually isolated. When we isolated the ketone from artificial mixtures with anisole by using the same experimental technique, we could recover 90% of the ketone. We do not think it worth while to apply a correction of approximately 10% to our quoted yields, but it is clear that the actual yields are in excess of those given.

We also showed in Part I that a reagent containing only acetic and perchloric acids is not an acetylating agent. We decided to study the possibility of dehydrating the acetic acidium ion to the acetylium ion. For this purpose we treated the reagent in the cold with phosphoric oxide, and then with anisole at room temperature. In spite of the fact that the reaction mixture was heterogeneous, we had no difficulty in isolating 15% of *p*-methoxyacetophenone. We suggest that the reaction involved is:

$$AcOH_2^+ + P_2O_5 \longrightarrow Ac^+ + 2HPO_3$$

rather than the sequence

$$2AcOH + P_2O_5 \longrightarrow Ac_2O + 2HPO_3; \quad Ac_2O + HClO_4 \longrightarrow Ac^+ + ClO_4^- + AcOH.$$

We have also discovered that when a little 72% perchloric acid is added to an excess of acetic anhydride, and the mixture kept at room temperature, the resulting acetylium ions acetylate the mixture of acetic anhydride and acid (produced in the original reaction) since a positive iodoform reaction can be obtained after 1 hour. We have not yet been able to identify the crystalline reaction product which separates from such mixtures in small amount, but it must clearly contain the group $CH_3{\cdot}CO{\cdot}C\leqslant$. The same reaction occurs more slowly at 0°. We have also shown that acetylium perchlorate will react rapidly (within 10 minutes) with acetic

anhydride to give presumably the same compound but that reaction with acetic acid does not occur within 18 hours at room temperature: addition of acetic anhydride to the mixture results in the rapid production of the iodoform-producing substance.

Experimental.

Materials.—Acetyl chloride and acetic anhydride were AnalaR reagents. Acetic acid was purified by Orton and Bradfield's method (*J.*, 1924, 960). Anisole, nitromethane, and methyl cyanide were all dried and redistilled. Silver perchlorate was dried over phosphoric oxide in a vacuum desiccator containing also a dish of solid potassium hydroxide: it was not used in any experiment until a perfectly clear solution in benzene was obtained. To ensure that no absorption of water occurred during the weighing of the salt, the required amount was left in the reaction flask in the desiccator for at least 24 hours and then re-weighed before use.

Experiments in Absence and Presence of Acetic Acid.—Acetyl chloride (0·025 g.-mol.) alone or a solution in the appropriate amount of glacial acetic acid was added over a period of 15—17 minutes to a cooled solution of silver perchlorate (0·025 g.-mol.) in anisole (0·1 g.-mol.) so that the temperature remained between 0° and 5°. In those cases where nitromethane (or methyl cyanide) was used (see Table and Introduction) this was mixed with the silver perchlorate solution. The reaction mixture was kept at 0—5° for 45 minutes after the addition of all the acetyl chloride and was then poured on ice.

In all the above and subsequent experiments the customary precautions for the exclusion of moisture were taken.

Experiments in Presence of Acetic Anhydride.—Silver perchlorate (0·05 g.-mol.) was dissolved in a mixture of acetic anhydride (0·15 g.-mol.) and anisole (0·2 g.-mol.), and the appropriate amount of glacial acetic acid was then added. In experiments where nitromethane (or methyl cyanide) was used, the above solution was diluted further with the appropriate amount (see Table). After the solution had cooled to 0°, acetyl chloride (0·05 g.-mol.) was added dropwise with shaking, over a period of 15—20 minutes so that the temperature remained between 0° and 5°. Frequently on complete addition of the acetyl chloride the temperature rose uncontrollably to *ca.* 8°, especially in the more concentrated mixtures, where efficient mixing of the stiff paste was difficult. After being kept for a further 45 minutes at 0—5° the reaction mixture was poured on crushed ice (150—200 g.), this stage being marked by a transient violet coloration of varying intensity.

Isolation of p-Methoxyacetophenone.—In both the above procedures the silver chloride in the reaction mixtures was dissolved by the cautious addition of the minimum amount of aqueous ammonia (*d* 0·88), and the residual oil extracted with ether. The ethereal extract was washed with dilute (2*N*.) ammonia solution and then twice with water. The dried (Na_2SO_4) extract was then evaporated and the residue fractionated at about 4 mm., whereby a good separation of the ketone, b. p. 110—115°/3·8 mm., from unchanged anisole was obtained. The ketone solidified on cooling and was frequently identified as its 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 222°.

Synthetic mixtures of *p*-methoxyacetophenone and anisole were submitted to the same treatment. The recovery of ketone was never less than 90% and occasionally was as high as 93%.

Comparison of Acetylium Perchlorate and Perchloric Acid–Acetic Anhydride Mixtures.—(*a*) A mixture of acetic anhydride (0·155 g.-mol.) and nitromethane (53·0 g.) was cooled to below 0° and 72% perchloric acid (3·5 g. = 0·025 g.-mol. of $HClO_4$) added over a period of 18 minutes so that the temperature remained between 0° and 5°. Anisole (0·1 g.-mol.) was then added during 3 minutes and the mixture kept at 0—5° for a further 45 minutes. The deep orange-red reaction mixture was poured on crushed ice (*ca.* 150 g.), and the resulting oil extracted with ether. The ethereal solution was washed twice with dilute ammonia solution (2*N*.), and twice with water, and was then dried (Na_2SO_4). Distillation (as above) gave *p*-methoxyacetophenone (5·2 g. = 0·035 g.-mol.), identified as the 2 : 4-dinitrophenylhydrazone.

(*b*) Silver perchlorate (0·025 g.-mol.) was dissolved in a mixture of acetic anhydride (0·075 g.-mol.) and nitromethane (53·0 g.), and the solution cooled to below 0°. Glacial acetic acid (0·135 g.-mol.) mixed with acetyl chloride (0·025 g.-mol.) was added during 17—18 minutes, the temperature being kept between 0° and 5°. Anisole (0·1 g.-mol.) was then added (3—4 minutes) and the mixture kept for 45 minutes at 0—5° before being poured on crushed ice. *p*-Methoxyacetophenone (5·3 g. = 0·035 g.-mol.) was isolated as described above.

Dehydration of Acetic Acidium with Phosphorus Pentoxide.—72% Perchloric acid (7·0 g. = 0·05 g.-mol. of $HClO_4$) was cautiously added to acetic anhydride (0·11 g.-mol.) so that the temperature did not exceed 35°. The solution was cooled to 0° and phosphoric oxide (0·05 g.-mol.) was added gradually with constant shaking followed by anisole (0·1 g.-mol.), so that the temperature remained between −2° and 1°. The colourless mixture was kept at 0° for 45 minutes and then allowed to warm to room temperature whereupon it developed a pink colour. After 22—23 hours the mixture consisted of two layers, a deep orange-red liquid (*A*) and a brownish, glassy lower layer (*B*). The liquid (*A*) was poured on crushed ice and the material (*B*) was shaken with crushed ice until decomposed whereby an oil separated. The combined oily products were extracted with ether, a small amount of tarry material separating at this stage. After the ethereal solution had been washed with sodium carbonate, sodium hydroxide, and with water, it was dried (Na_2SO_4) and evaporated. Fractionation of the residue gave anisole (0·058 g.-mol.) and *p*-methoxyacetophenone (2·3 g. = 0·015 g.-mol.), m. p. 34—37°, together with non-distillable material (1·1 g.).

Acetylation of Acetic Anhydride by Acetylium.—(*a*) 72% Perchloric acid (1 c.c.) was added to acetic anhydride (100 c.c.) and the mixture left at room temperature. The mixture soon became brown and after four days stout needles began to separate.

Such solutions gave a positive iodoform reaction when sodium hydroxide was used in the cold after 30 minutes. The development of colour was retarded by addition of acetic acid.

(*b*) Acetyl chloride (1·0 g.) was added to silver perchlorate (2·6 g.) dissolved in acetic anhydride (25 c.c.). The mixture rapidly became coloured and a positive iodoform reaction was obtained within 10 minutes. Crystalline material separated slowly from the solution. The same phenomenon has been observed by Winter (private communication).

(*c*) Acetyl chloride (1·0 g.) was added to silver perchlorate (2·6 g.) dissolved in glacial acetic acid (25 c.c.). The mixture remained colourless during the subsequent 21—22 hours and did not give an iodoform reaction. Addition of acetic anhydride (10 c.c.) to the mixture caused a faint positive iodoform reaction to be obtained after 30 minutes.

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418. *Carbon Formation in Flames.*

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The fundamental chemical processes leading to carbon formation in hydrocarbon flames are not understood. In simple diffusion flames of acetylene in air or oxygen examined at low pressure, carbon formation depended markedly on pressure, in agreement with observations of other authors. For hydrocarbon gases during pyrolysis and in the pre-heating zone of a flame, continuous absorption in the ultra-violet region spread as the temperature was raised. This effect is probably related to carbon formation. None of the results can be fully accounted for by existing theories, however, and two alternative explanations are tentatively suggested.

THE formation of carbon particles in hydrocarbon flames is well known and of considerable industrial importance. Although the technique of controlling carbon formation has been successfully developed in some cases, the fundamental chemical processes involved are not understood.

Data in the literature are meagre. Davy first attributed the luminosity of hydrocarbon flames to the presence of incandescent carbon particles; early studies by Marchand, Berthelot, Lewes, Bone, and others on how these carbon particles occur in the flame are summarised by Bone and Townend ("Flame and Combustion in Gases," Longmans, Green & Co., 1927, p. 406). More recently Rummel and Veh (*Arch. Eisenhüttenwesen*, 1941, **14**, 489) considered the conditions required for carbon formation and suggested that the soot particles are precipitated as residual carbon skeletons of big aromatic or polycyclic molecules. These molecules are formed in the gas phase, and largely dehydrogenated, during pyrolysis of the hydrocarbon in the flame. The greater tendency of aromatic fuels to deposit soot, and the similarity of the graphitic structure of this soot to the structure of the higher homologues of benzene, appear to support this hypothesis. On the other hand, a spectroscopic study of ethylene flames led Smith (*Proc. Roy. Soc.*, 1940, *A*, **174**, 110) to suggest that carbon deposition is due to the polymerisation of C_3 molecules; he recalled the work of Klemenc, Wechsberg, and Wagner (*Z. physikal. Chem.*, 1934, **170**, 97) on the thermal decomposition of C_3O_2 in which C_2 was formed and recognised by its absorption spectrum but rapidly polymerised to normal solid carbon.

The tendency of organic substances to smoke on burning freely in air has been examined by Clarke, Hunter, and Garner (*J. Inst. Petroleum*, 1946, **32**, 627). They show that with hydrocarbons it is not merely a question of the C/H ratio: other factors concerning the structure of the molecule are involved. Thus the tendency of normal paraffins to smoke is relatively slight and increases with increasing chain length, but it is greater with branched-chain paraffins than with their normal isomers. Unsaturated compounds give appreciably more smoke than do the paraffins, but there is a different variation with structure. Increase in chain length of the olefin results in decreased smoke formation, as does an increase in the number of carbon atoms in the diolefin, benzene, and naphthalene series. For compounds containing oxygen, the content of this element is also of significance. In general, increased oxygen content results in a decreased tendency to smoke, provided that the hydrocarbon portion of the molecule does not exert an over-riding effect. Methyl alcohol for example does not form any carbon.

The voluminous literature on the pyrolysis of hydrocarbons shows that carbon and hydrogen are the ultimate products of a purely thermal process. In diffusion flames the rôle of pyrolysis is undoubtedly significant, and in pre-mixed gas flames the presence of oxygen during the pre-heating stage profoundly alters the conditions in which carbon is formed. Gaydon and Whittingham (*Proc. Roy. Soc.*, 1947, *A*, **189**, 313) described the influence of oxides of sulphur

on the luminosity of pre-mixed gas flames; the effect, which is apparently catalytic, was not observed by us in diffusion flames. These and other facts bearing on the problem seem to us too limited experimentally for solution of this complex problem.

The first step in the present investigation was consideration of experimental methods. Diffusion flames have been burned at low pressure, and a number of new features relating to carbon formation have been observed, including a pressure limit below which no carbon was obtained. This may be related to Smith's observations (*loc. cit.*) that sooting was more pronounced in an ethylene–air flame at pressures greater than one atmosphere. The size and uniformity of the particles which we collected from the luminous zone of a diffusion flame have been examined under an electron-microscope, and absorption spectroscopy has been applied to hydrocarbons during pyrolysis and in the pre-heating zone of a flame. Many of the results obtained from these experiments cannot be adequately explained by existing theories and an alternative is suggested which is admittedly speculative.

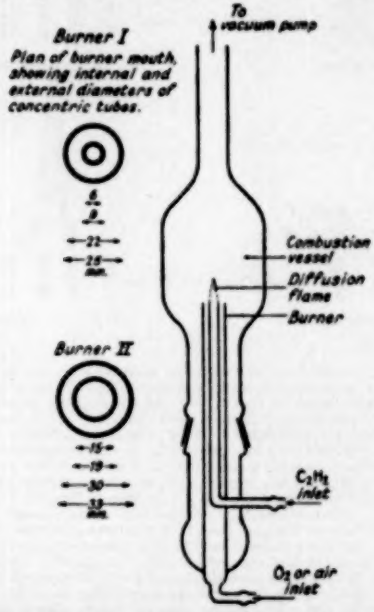
The investigation has been restricted to diffusion flames in their simplest form. The majority of technical applications of combustion employ diffusion flames although the conditions in the flames are complicated by turbulence.

Experimental.

Examination of Diffusion Flames at Reduced Pressures.—Careful observations were made of the changes occurring in the reaction and the luminous zone of a non-aerated gas flame on a circular burner

Fig. 1.

Apparatus for the study of diffusion flames at low pressures.



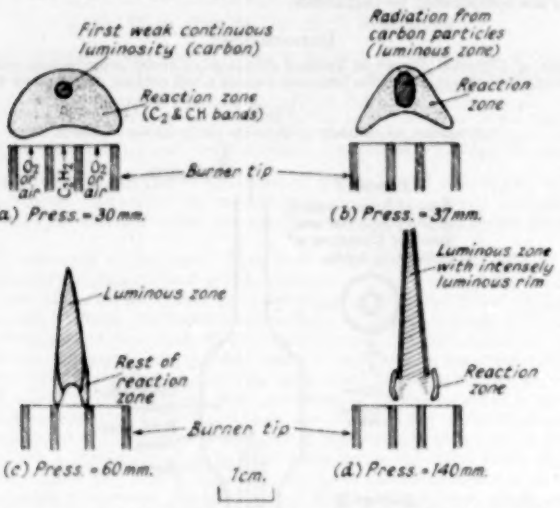
when the external pressure was reduced. For work at low pressure the following technique was adopted: A large glass vessel (Fig. 1) was connected to a powerful vacuum pump. Two concentric glass tubes entering at the bottom through a ground-glass joint and passing vertically into the vessel, formed the burner, and the dimensions were such that the ratio, area of annulus : area of inner tube, was very nearly equal to the ratio, volume of air/sec. : volume of fuel/sec. The linear velcities of the air and the fuel gas were thus approximately equal. In contrast to conditions in an open gas jet burning in an unlimited amount of still air it was possible to change the mixture strength by changing the dimension

of the burner and still to keep the linear velocities of air and gas equal, thus avoiding frictional problems. With this arrangement the flame burned very steadily and was surrounded by its own exhaust gases. The Reynolds numbers were very low and there was no turbulence.

In experiments with acetylene and air in burner I (see Fig. 1) the volumetric flows at N.T.P. were 1 and 11·9 c.c./sec. respectively. The corresponding mass flows were kept constant and independent of the pressure in the combustion vessel, so that as the pressure was reduced the velocity of the emergent gases increased. After ignition the reaction between the two concentric streaming gases depended on interdiffusion. Since the diffusion coefficient was inversely proportional to the pressure, the rate of mixing increased as the pressure was reduced. In this way the height of the diffusion flame (dependent on both the gas velocity and the diffusion rate) should theoretically remain constant, if diffusion is the rate-determining process of the combustion (Wolfhard and Parker, *Proc. Physical Soc.*, 1949, **62**, 722, and unpublished work). The diffusion flame at reduced pressure behaved as predicted, as long as no carbon formation occurred, but, as described below, carbon formation depended markedly on the pressure. The reaction mechanisms for the oxidation of acetylene molecules and for the burning of carbon particles are different, which in turn influences the height of the flame.

FIG. 2.

Special features of an acetylene–air diffusion flame at low pressures.



The lowest pressure at which burning could be maintained with this mass flow in burner I was 29 mm. Hg. At lower pressures the flame suddenly lifted off the burner. The features of the flame at various pressures are shown in Fig. 2*a*—*d*. At the limiting pressure, the reaction zone was cone-shaped, and radiation consisted only of the C_2 and CH bands in the visible region together with a weak continuum from electron recombination. The C_2 bands were slightly stronger in the upper part of the cone, and the reverse held for the CH bands. Fig. 1*a* depicts the flame at 30 mm. pressure: the appearance was much the same except for a small red patch due to carbon particles nearly in the centre of the cone. At 37 mm. (Fig. 2*b*) the cone remained of about the same size and shape, but the red patch was larger, reaching the upper boundary of the flame. At 60 mm. (Fig. 2*c*) the blue cone became smaller but remained essentially the same in length, while the red centre (caused by radiation from carbon particles) was level with the base of the blue cone at the bottom and extended above the blue cone at the top. The growth of the carbon region beyond the blue cone was rather sudden and effected in some cases by a pressure change of only a few mm., and the overall height of the flame was doubled or even trebled. At 140 mm. (Fig. 2*d*) the blue cone was small and unimportant but the carbon region was considerably changed. Instead of being very uniform in intensity, as at 60 mm. pressure, it had a fine structure and a more intense rim. The region was no longer closed but was open at the top, and at 180 mm. this opening increased so much that soot could be seen escaping at the top. At 270 mm. the rim of the luminous cone had become very sharp indeed and the flame looked like a hollow luminous cylinder when viewed from above or below. At 340 mm. a new feature was observed: the sharp rim of the luminous carbon region was surrounded by a thin pale luminous skin which extended to the base of the flame.

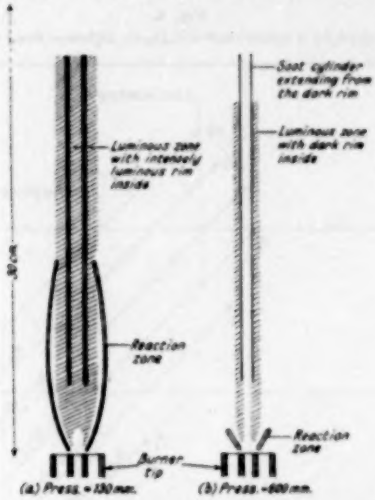
An increase in mass flow to 16 c.c. of acetylene and 190 c.c. of air per second made the flame much taller. Fig. 3*a* illustrates the flame at a pressure of 130 mm. (cf. Fig. 2*b*). The blue cone was about

sixteen times as high as before and the carbon region was 30 cm. high. The sharp brightly luminous rim which gave the flame a hollow appearance already had a rather thick pale luminous skin around it, while inside the radiant cylinder the luminosity was weak and may have been an optical effect caused by overlapping luminous layers. At 220 mm. the luminous rim, hitherto very bright, became black. The pale luminous skin was then the only source of radiation and it was lined inside by the thin deep black layer in place of the former sharp brightly luminous rim. On top of the flame, where the luminosity faded away, the black thin layer continued into a hollow cylinder of soot. Again the blue cone had become small and unimportant. Fig. 3*b* shows these features for a pressure of 600 mm.

In experiments in which oxygen was used instead of air it was possible to burn the flame at much lower pressures with the pump capacity and burners available. It was clear too that as long as no carbon appeared the flame height was essentially independent of the pressure and proportional to the mass flow in accordance with diffusion considerations (Burke and Schumann, *Ind. Eng. Chem.*, 1928, **20**, 998).

FIG. 3.

More features of the acetylene–air diffusion flame at low pressure (increased mass flow).


Soot cylinder extending from the dark rim
Luminous zone with dark rim inside
Luminous zone with intensely luminous rim inside
30 cm.
Reaction zone
Reaction zone
Burner tip
(a) Press. = 130 mm.
(b) Press. = 600 mm.

The oxygen flames, too, were much hotter and the burner rim became red hot, which led to cracking of the fuel on the rim of the inner tube. A carbon deposit grew in branching form and this growth was sometimes very rapid and built up 1—2 mm. in 10 seconds. Finally a network of branches formed a cone which restricted the acetylene flow. Examined under the microscope this carbon was obviously different from soot: it had a smooth shiny surface similar to that of methane carbon found on the walls of the reaction vessel after the pyrolysis of methane and generally agreed with the description of vitreous carbon given by Ephraim ("Textbook of Inorganic Chemistry," 4th Edn., 1943, p. 137). This suggests a difference in the mode of formation and it seems that soot particles may be formed in the gas phase, whereas vitreous carbon and methane carbon are the products of surface reactions.

Low-pressure Termination of Carbon Formation.—Observations were made on the limiting pressure of carbon formation for an acetylene–oxygen diffusion flame in burner II. The dimensions of this burner were such that the mass flow of acetylene and oxygen were in stoicheiometric proportions, and the linear velocities of the two gases were equal, as with burner I. In Fig. 4 the results are shown by plotting (on a log–log scale) the total pressure in the combustion vessel and the mean velocity of the gas before it reached the flame. For a given mass flow a straight line inclined at 45° was obtained. The 0·5 c.c./sec. acetylene line terminates at 43 mm. pressure; at this pressure the flame reached its minimum point for self-propagation. The heat loss by conductivity and diffusion reached a value such that the flame was unable to persist. For the 1·0 c.c./sec. acetylene mass flow line the minimum point moves towards lower pressures; for the 4·0 c.c./sec. line the minimum point was beyond the pump capacity.

In these results there seemed to be one general fact, that from the minimum point and over a certain pressure range there was no luminosity due to carbon particles. When, however, the minimum point was low enough—this required a mass flow of about 2 c.c./sec. or more of acetylene—carbon formation set in at about 19 mm. pressure and above. This value (*A* in Fig. 4) seemed to be a constant for stoicheiometric acetylene–oxygen mixtures and was independent of the mass flow over the range tested (2—16 c.c./sec. of acetylene; reduced to N.T.P.). It is of course possible that this pressure limit depends

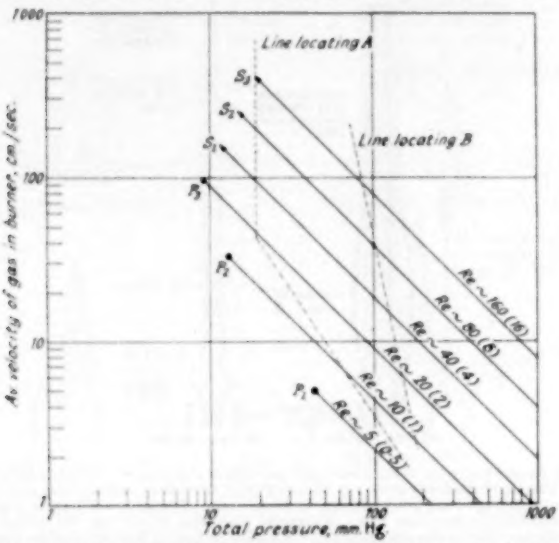
to some extent on the overall burner size. Moreover difficulty was sometimes experienced in observing the low pressure limit of carbon formation, because even at pressures lower than 19 mm. the flame was very bright through the presence of CH and C_2 bands and some electron recombination continuum. The first weak luminosity caused by carbon formation could usually be located more readily by using a pocket spectrograph. The fact that carbon formation ceased at the same pressure over a wide range of mass flows seems to indicate a real low-pressure limit for this burner size.

Another characteristic of the flame, marked *B* in Fig. 4, is the point at which the luminous cone was hollow and accompanied by the onset of very marked soot formation. The line locating *B* is inclined to the line locating *A* (the first appearance of luminosity) and forms a triangle within which the luminosity is due to incandescent carbon particles. All of these are ultimately burned. Free soot formation occurs to the right of this triangle.

If oxygen was used with acetylene in burner I, the oxygen supply was virtually unlimited and the pressure limit of carbon formation was about 80 mm. The flame was very bright indeed and carbon growth very rapid. The luminous cone was mostly hollow but no free soot was observed. The carbon apparently burned away in the excess of oxygen.

FIG. 4.

Stability region for a stoicheiometric C_2H_2–O_2 diffusion flame (Burner II).

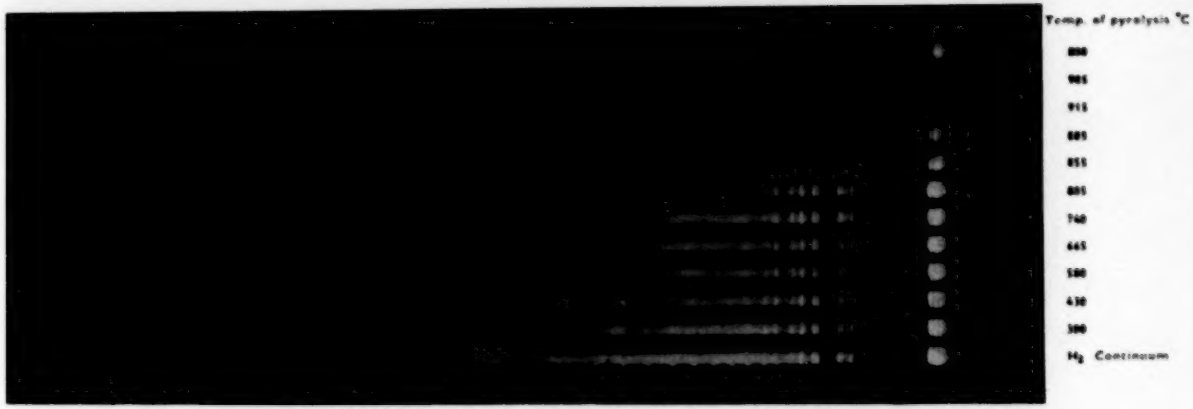


P_1, P_2, and P_3 indicate the "minimum points" for propagation of the flame. S_1, S_2, and S_3 indicate the lowest pressures the pump could achieve. Numbers shown in parentheses are the mass flows of the C_2H_2 in c.c./sec. at N.T.P. Re indicates the Reynolds number of the fresh gas.

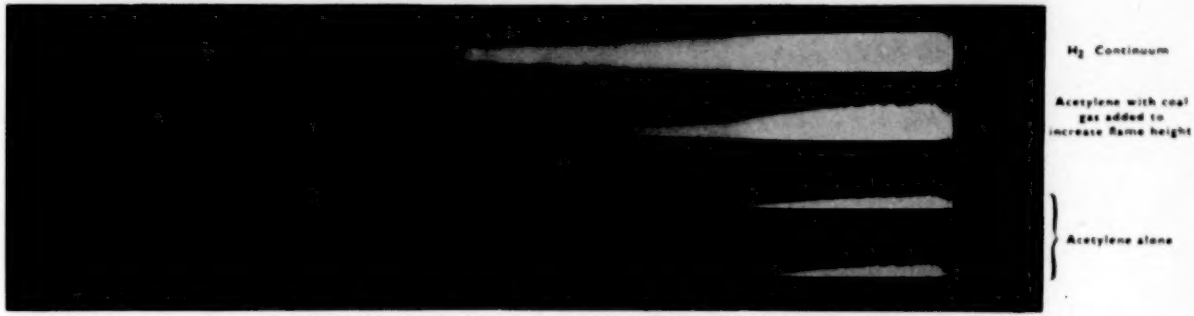
In diffusion flames with oxygen the bright rim in the luminous zone never underwent the inversion to opaque soot which was so characteristic in the air diffusion flame, though in other respects the flames were similar. The oxygen flames were of course much brighter.

The air diffusion flame of acetylene had a low-pressure limit of carbon formation at about 30 mm. and again a luminosity triangle similar to that described for the oxygen flame could be contructed by plotting the results in the manner of Fig. 4.

Size of Carbon Particles in a Diffusion Flame.—To get some information on the size of carbon particles in a diffusion flame a standard Hefner candle was used containing amyl acetate. The carbon particles were collected on a copper grid or a wire passed rapidly through the flame and subsequently photographed under an electron microscope. The Hefner candle could be made smoky or non-smoky by adjusting the height of the wick. In a non-smoky flame all carbon particles (which built into filaments or chains on the sampling grid) were nearly equal in size, approx. 100 A. In a smoky flame, however, some large particles of approx. 500 A. were also found. The latter result must be treated with some reserve because it is difficult to obtain a representative sample from the grid, and the ratio of small to big particles varied considerably in different parts of the grid. Two other facts were apparent: (1) the particles collected near the top of the flame were similar in size to those collected near the base,



(a). ABSORPTION SPECTRA OF ETHANE AT ELEVATED TEMPERATURES



(b). ABSORPTION SPECTRA OF GAS EMANATING FROM A FISH-TAIL BURNER

FIG. 7. ABSORPTION SPECTRA OF HYDROCARBONS.

and the size was not noticeably affected when the candle was burning very brightly in pure oxygen; and (2) when the particles collected on a grid were heated in a hydrogen flame some increase in size seemed to take place. The latter fact however is again subject to the limitations of the method.

The most reliable and significant fact of this analysis is therefore the uniformity of size of the particles throughout the luminous zone. In a non-sooty flame the particles do not grow and must have reached their final size before entering the luminous zone.

Absorption Spectroscopy.—The application of visible and ultra-violet absorption spectroscopy to pyrolysis has not been attempted hitherto, as far as the authors are aware. This is understandable since all the lower hydrocarbons (except the aromatics) are transparent even in the ultra-violet region, and little useful information would be expected from the method. Spectro-analysis is of course used in photolysis, *e.g.*, for acetylene (Dunicz, *J. Amer. Chem. Soc.*, 1941, **63**, 2461), but the conditions are very different from those of pure pyrolysis. Carbon formation in flames which results in the production of incandescent soot particles with an extensive continuum limits this method for the present purpose to an examination of the regions below the luminous zones. Measurements of absorption in a benzene diffusion flame on a Hefner candle indicated that the benzene bands disappear a short distance above the wick and before the vapour reaches the luminous zone of the flame. No other bands appeared in their place.

The absorption spectra of straight-chain and aromatic hydrocarbons were then examined, both during pyrolysis and in diffusion flames of more suitable dimensions. Several new facts were observed which may be relevant to the process of carbon formation.

For the pyrolysis experiments the arrangement was as follows: A quartz tube, 40 cm. long and 2 cm. in diameter, was closed at each end by plane quartz windows. The tube was inserted in a furnace, 33 cm. long, which could be heated to 1000°. Hydrocarbon gases could be admitted to the tube through inlets at both ends and leave the tube again from an outlet at the centre. This arrangement had two special features, first, the inlets being at the ends prevented condensation of pyrolysis products on the plane quartz windows, and, secondly, the outlet pipe was brought out of the furnace again and the products passing through it were burnt as a diffusion flame at the end. Ultra-violet light from a hydrogen discharge tube of the low-tension type was passed in a parallel beam through the quartz tube and then focussed on the slit of a medium quartz spectrograph (Hilger E3). The absorption spectra were obtained for each of a number of different hydrocarbons flowing continuously at a fixed rate (approx. 5 c.c./sec.) through the tube at various temperatures. The results were as follows.

Ethane. From room temperature to 580° there was no absorption in the available wave-length range, *viz.*, 2150—6000 A.; the tube was clear and there was no change in the outlet tube or the flame burning on the end of it. At 665° a continuous absorption began from the short wave-length end of the spectrum and the hydrogen continuum was absorbed up to 2450 A.; no change occurred in the outlet pipe or the end flame. At 805° the absorption had increased to 2800 A. and a mist was noticed in the cool part of the outlet tube; the luminosity of the flame on the outlet pipe had also noticeably increased. At 855° absorption was complete up to 3700 A.; condensation in the outlet tube was very marked and the flame was so luminous that it began to become sooty. At 885° absorption had reached 4200 A. and the hydrogen continuum seen through the tube appeared clear but slightly yellowish owing to the onset of absorption in the visible region. At 915° the absorption reached 5500 A. and the continuum was completely absorbed in the ultra-violet blue and the green region.

On lowering the temperature of the furnace the absorption decreased again in the reverse order, which indicated that the effect was real and not due to some extraneous cause such as condensation on the windows.

This continuous absorption which increases with temperature is a major feature of thermal reaction of hydrocarbons and seems to have been overlooked hitherto. It was found for all the hydrocarbons investigated (*viz.*, methane, ethane, butane, ethylene, acetylene, and benzene) and also for ethanol, but not for methanol.

The spectra obtained for ethane are shown in Fig. 7*a*.

Methane. A continuous absorption began at a higher temperature (870°) than with ethane (665°) but increased more rapidly with temperature. At 980° it had already reached 3300 A., while at 1000° absorption was complete in the ultra-violet. The effect of pyrolysis on the diffusion flame at the outlet was very interesting. The luminosity of the flame did not change much with the furnace temperature and the mist formed by condensation of the products of pyrolysis entered the flame. Some of the mist became radiant before it reached the true luminous zone of the flame and appeared as intensely luminous streaks which passed right through the luminous zone and escaped as soot from the top of it. It is certain that the contact times in the flame are insufficient to give soot particles of this size and they must be produced during an extensive thermal reaction in the furnace.

Ethylene. The continous absorption of ethylene began at about 400° and was spread over the ultra-violet region up to 4600 A. at 750°. The process extended over a wider range than with methane.

Acetylene. This began to absorb at still lower temperatures than ethylene. The effect of pyrolysis can only be distinguished above 2300 A. since acetylene absorbs in the region 2000—2400 A. at ordinary temperature. Moreover, at elevated temperatures higher vibrational levels are activated (an effect which does not appear to have been recorded hitherto) and even at 100° some increasing absorption begins in the far ultra-violet for that reason. At 330°, however, there was an absorption which could be attributed to pyrolysis and the whole of the ultra-violet region was affected within the temperature range 330—500°.

Benzene. This has a strong absorption band at about 2600 A., which may be useful for observation of the effects of pyrolysis or of combustion. The experimental arrangement was not suitable for following the disappearance of this band (cf. experiments with the Hefner candle) because relatively cool benzene

vapour was always present at the two ends of the tube. It was, however, possible to see whether other aromatic compounds were formed through decomposition or polymerisation of the benzene during pyrolysis, since all more complex aromatic compounds have bands at longer wave-lengths than benzene. (The last statement must be slightly qualified because present knowledge is very limited on the absorption spectra of these compounds in the gas phase but it is true of spectra obtained from solutions.) No unidentified bands were observed between 2700 and 4000 A. in any of the spectra and it is concluded that the benzene molecules decompose before polymerisation to polycyclic compounds.

The experiments with benzene were carried out in two ways. At first a stream of nitrogen, saturated with benzene vapour at room temperature, was passed through the quartz tube in the furnace. The concentration of benzene was relatively low and the absorption was not too strong, so that the short-wave side of the 2600 A. band could be examined. It must be remembered of course that the thermal reaction is also retarded at a low concentration of benzene. Interpretation of the spectra is complicated by the strong temperature influence on the natural absorption spectrum of benzene. Higher vibrational levels appear to be activated and the bands spread to longer wave-lengths, though not beyond about 2750 A. Near 2300 A. a small continuous absorption originating in benzene exists, which becomes stronger even at 250°, and it is possible that more than one effect is really observed. At 750° a continuous absorption set in beyond 2700 A. and this was definitely due to thermal reaction. Other experiments were made with pure benzene vapour and precautions were taken to prevent condensation of the vapour in the supply tubes and at the cool ends of the pyrolysis tube. Continuous absorption beyond 2800 A. began to increase with certainty at about 500° or even below, and spread slowly to 3350 A. at 800°.

FIG. 5.

Upper wave-length limits of strong absorption at higher temperatures.

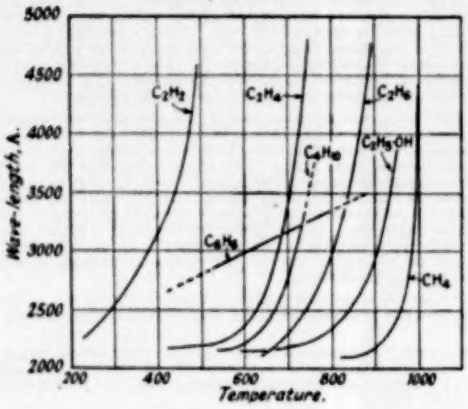
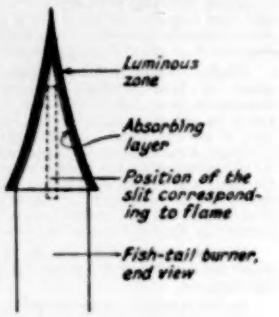


FIG. 6.

Arrangement of fish-tail burner for absorption experiments.



Methyl alcohol. This compound was included because it is well known that its flame contains no luminous carbon or soot. The pyrolysis has also been thoroughly investigated (Fletcher, *Proc. Roy. Soc.*, 1934, *A*, **147**, 119), and formaldehyde has been identified as an intermediate product. In these experiments, using very pure methanol to start with, no continuous absorption was observed at any temperature up to 1000° and the outlet flame did not acquire luminosity. Above 600° formaldehyde bands appeared and remained up to 900°, whereafter they began to disappear again. The maximum strength of these bands was observed at about 700—800°. This result is very important for the present investigation and also suggests a good method for studying the decomposition reaction in detail.

Ethyl alcohol. The luminosity of an ethyl alcohol diffusion flame is comparable with that of methane and ethane. The vapour was passed into the pyrolysis tube with the usual precautions against condensation. A continuous absorption began at about 600° and had eliminated nearly all the ultra-violet light by about 960°. Formaldehyde bands appeared initially at 550° and afterwards in strength comparable with those observed in the methanol experiments. This might be explained by assuming that the C–C bond is broken first

$$H_3C\text{-}CH_2\text{-}OH \longrightarrow CH_4 + CH_2O$$

and that the formaldehyde then decomposes further while the methane is pyrolysed. Continuous absorption, however, began at a somewhat lower temperature than in the experiments with methane and was more in accord with that of ethane. Formation of ethane through a bimolecular reaction such as $2H_3C\text{-}CH_2\text{-}OH \longrightarrow C_2H_4 + 2CH_2O + H_2$ may explain the similarity.

In Fig. 5 the wave-length at which strong absorption began for each hydrocarbon has been plotted against the temperature of pyrolysis. The curves are of course relative and depend, *inter alia*, on the

intensity of the light source. The latter was kept constant and the same lamp was used for all experiments. The curves indicate the thermal stability of the various substances, but the reason for the different shapes is unknown and benzene is clearly very different from the others.

Another important observation in these experiments was the absence of characteristic aromatic absorption bands during the pyrolysis of ethylene or acetylene. Since some aromatic compounds are readily formed and can be isolated in the products after pyrolysis it seems clear that their formation from olefins or acetylenes is not a straightforward process.

Absorption Spectra of Diffusion Flames.—Since there may be some theoretical objection to considering the pre-flame reactions in diffusion flames as purely thermal processes, the results of the pyrolysis experiments were compared with similar spectroscopic measurements in a diffusion flame. In order to do this a large fish-tail burner, 10 cm. long and 1·3 cm. wide, was placed with its length along the axis of an optical system. Light from a hydrogen discharge lamp passed over the top of the burner and lengthwise through the tunnel formed by the inclined sides of a flame on this burner and was brought to a focus on the slit of the spectrograph by means of a quartz–fluorite achromatic lens. An end view of the burner and flame is shown in Fig. 6 and the portion focussed in the slit is indicated by the dotted rectangle. A uniform flame was obtained by filling the burner with glass beads which smoothed the gas flow and flickering was avoided by placing the burner in a channel between two bricks.

With this arrangement absorption measurements included the long gas tunnel under the luminous mantle of the flame together with the two luminous layers at each end. The absorption due to the end layers could be estimated by turning the burner through 90° and measuring the absorption of two similar luminous layers and a relatively short gas space. With an acetylene or a benzene diffusion flame (in which the burner was kept at a temperature above the b. p. of benzene) it was observed with the naked eye that, just before reaching the luminous zone, the gases absorbed all visible light from the hydrogen lamp and a dark layer was visible under the luminous zone.

Fig. 7*b* shows a spectrum of the H_2 continuum partly absorbed in the acetylene flame. As indicated in Fig. 6 the lower part of the spectrum coincides with the base of the flame. There is very little absorption at this point but on proceeding up the flame, *i.e.*, also up the spectrogram, the absorption increases from the short-wave into the ultra-violet and finally reaches the visible region. The overall effect is a wedge-shaped spectrogram caused by increasing absorption by the gas from the top of the burner to the reaction zone. Other gases behaved similarly, especially ethylene. Methane and ethane gave rather tall flames which were difficult to keep steady with the apparatus used, but sufficient evidence was obtained from them to confirm the result. Since the temperature of the gases increases from the burner to the reaction zone the effect observed is probably directly comparable with the absorption effect on pyrolysis, and substantially the same processes occur.

Discussion.

The principal results of our experiments can be summarised as follows :

(*a*) A diffusion flame can probably exist at any pressure provided that conditions of burner size and mass flow are suitably adjusted, but carbon formation in the flame depends markedly on pressure.

(*b*) Carbon deposits on the mouth of the burner, which formed very rapidly under certain conditions, were of a hard vitreous type, different from soot particles collected from the luminous zone of the flame.

(*c*) Carbon particles in the luminous zone of a non-smoky flame are uniform in size and do not grow in the luminous zone.

(*d*) The absorption spectra of hydrocarbons undergoing pyrolysis show an increasing continuous absorption spreading from the far ultra-violet and towards the visible region as the temperature of pyrolysis is raised. The relative temperatures at which this occurs for different hydrocarbons are in agreement with their known thermal stabilities. Similar effects were observed with ethyl alcohol but methyl alcohol behaved differently.

(*e*) Measurements in the pre-heating zone of a diffusion flame revealed similar absorption effects which increased from the burner mouth to the top of the zone.

(*f*) Measurements of absorption in a benzene diffusion flame on a Hefner candle indicated that the benzene bands disappeared a short distance above the wick and before the vapour reached the luminous zone of the flame. No other bands appeared in their place.

The similarity between the observed changes in absorption spectra of hydrocarbons in the pre-heating zone of a flame and those during pyrolysis supports the view that pyrolysis is an essential factor in combustion processes of diffusion flames.

There is a marked difference in the conditions under which carbon formation occurs in pre-mixed flames (*e.g.*, a Bunsen flame) and in diffusion flames. Although the latter are more important for the purpose of this investigation, pre-mixed flames have been more fully studied in the past (Klaukens and Wolfhard, *Proc. Roy. Soc.*, **1948**, *A*, **193**, 512; Gaydon and Wolfhard, *ibid.*, **1948**, *A*, **194**, 169). The truly pre-mixed flame which will be considered is the inner cone of the Bunsen flame. The velocity of the pre-mixed fresh gas is much greater than that of the gas in the diffusion flame. The hydrocarbon fuel molecules are subject to a high temperature

for a shorter time and the degree of decomposition before oxidation may be less. The fuel molecules are also in intimate contact with oxygen, whereas in diffusion flames, or at least in the core of a diffusion flame where carbon formation is strongest, the fuel molecules are first heated and later diffuse into a region of oxygen. The presence of a reaction zone around the diffusion flame acts as a barrier to the oxygen (Wolfhard and Parker, *Proc. Physical Soc., loc. cit.*, and unpublished work). The presence of oxygen may have in some cases a profound effect on carbon formation and retard it.

The flame front in the region of the inner cone of a pre-mixed flame can be dvided into two parts : (1) a pre-heating zone where no appreciable exothermic reaction occurs, and (2) a reaction zone characterised by light emission due mainly to C_2, CH, and OH bands. The reaction which is exothermic begins at about 800° for acetylene–oxygen and acetylene–air flames (Klaukens and Wolfhard, *loc. cit.*). Most hydrocarbons, however, undergo pyrolysis at a lower temperature and the fuel molecules probably undergo a certain amount of change before the exothermic reaction with oxygen begins, and the first steps in carbon formation may also occur before this. It should be stressed that the contact time for the thermal reaction is much shorter than in the corresponding diffusion flame.

Mention has been made of the presence of C_2 molecules in the inner cone, but the way in which they are formed is not understood. Since they generally occur very early in the zone they may be formed by pyrolysis, being actually produced before the main reaction with the oxygen molecules occurs. In fuel-rich flames the C_2 radiation is greater and, since carbon formation also increases, it has been suggested that condensation of the C_2 molecules is responsible (Smith, *loc. cit.*). At first sight this theory is attractive since the condensation process is strongly exothermic and will certainly occur if sufficient C_2 molecules are present. The number of C_2 molecules is probably very small, however, as indicated by the very low absorption coefficient in a pre-mixed acetylene–oxygen flame ($0 \pm 2\%$ abs.; Wolfhard, *Z. Physik*, 1939, **112**, 107) despite the normal transition probability measured by Brewer *et al.* (*J. Chem. Physics*, 1948, **16**, 797). Moreover, the fact that the C_2 disappears from the reaction zone earlier than CH and other intermediate molecules identified spectroscopically (Gaydon and Wolfhard, Faraday Soc. Discussion, 1947, **2**, 161) suggests that the C_2 molecule is very reactive and has little chance to survive and condense. Experimental results with a flat diffusion flame which has an absorbing layer of 5 cm. at atmospheric pressure (Wolfhard and Parker, *Proc. Physical Soc., loc. cit.*) support this argument. It was impossible to detect any C_2 absorption in flames of methane or coal gas with air or oxygen, only some weak C_2 band in emission located on the oxygen side of the luminous carbon region. The location of these bands strongly suggests that carbon formation does not depend on the existence of C_2 molecules. In view of these objections it seems unprofitable to attempt to interpret our results by this theory.

It has been suggested that the formation of benzene rings and polycyclic structures precedes the formation of carbon. Rummel and Veh (*loc. cit.*) postulate that the hydrocarbon undergoes pyrolysis in the flame with the formation of large polycyclic intermediate molecules which suffer dehydrogenation and finally condense as solid carbon residues. The graphitic structure of carbon particles resembles the molecular structure of the benzene ring, or more exactly that of its polycyclic homologues. Thus, if one benzene ring becomes attached to the next or if side chains on a benzene nucleus link up to give naphthenic and aromatic structures, and this process is repeated, one plane of the graphite structure is formed. By adding one plane to another and eliminating the hydrogen atoms between them, a particle of the kind found in a flame might be formed. This attractive theory is apparently supported by observations such as the greater tendency for aromatic fuels to smoke, and by the results of pyrolysis in which benzene and its homologues are formed by heat treatment of olefins and nearly every kind of hydrocarbon.

The absorption spectra which were obtained from the lower part of the benzene flame in experiments with a Hefner candle do not appear to support this theory. The flame was approximately double the height of the slit on the spectrograph and from the benzene absorption bands which disappear in the vertical direction it is concluded that the benzene is consumed in the lowest part of the flame. More important, however, is that no other absorption appears. Naphthalene, anthracene, etc., have molar absorption coefficients (measured in solutions) as great as that of benzene, and these absorption bands lie in the most convenient part of the spectrum. Hence it must be concluded that naphthalene, anthracene, etc., are absent. Their absence at this point is believed to be evidence against Rummel and Veh's hypothesis. The benzene flame from a Hefner candle is hollow and carbon formation occurs only in the cylindrical layer. There is an appreciable gap between the early disappearance of the benzene and the

appearance of the carbon particles, yet none of these aromatic intermediate products which should absorb so strongly is found in this gap.

It is true, of course, that the Hefner candle burning benzene is much more sooty than it is with amyl acetate or a paraffin, and the tendency for aromatic fuels to give coking troubles in combustion chambers is well known, but this is not necessarily evidence for the aromatic-ring-building theory of carbon formation. The tendency to smoke as measured in the soot lamp is actually smaller for the homologues of benzene than for benzene itself.

In pyrolysis of hydrocarbons, carbon and hydrogen are always the end products if the temperature and contact time are sufficiently great but there is no real evidence on the individual step leading to the deposition of carbon. Typical results with the simpler hydrocarbons are those of Tropsch and Egloff (Ellis, " The Chemistry of Petroleum Derivatives," Vol. II, 1937) for the pyrolysis of propane, ethane, and *n*-butane at 1100—1400° and 50 mm. pressure, in which the products are either hydrocarbons of fairly low molecular weight, such as ethylene, acetylene, and propylene, or carbon but nothing between. It is, however, certain that carbon particles of 100-A. diameter cannot be formed from these hydrocarbons in a single step and it is pertinent to ask whether there is any evidence of an intermediate product.

Before pursuing the question of an intermediate we shall discuss the nature of the carbon particles which form the end products. Hofmann and Dietrich (*Z. Elektrochem.*, 1936, **42**, 504) compared the breadth of the *X*-ray lines of various soot and carbon particles with the natural width of the lines on the *X*-ray diagram of Ceylon graphite. In this way it was possible to calculate the dimensions of the crystallites in the material. The height of the crystallites in soot from acetylene was 13 A. and the length was 21 A. Hence the carbon particles which were examined in this investigation and which had an irregular shape with an overall diameter of about 100—500 A. are probably not single crystals but are aggregates of many smaller crystals.

Hofmann and Dietrich also showed that the lattice constants are different: in Ceylon graphite $a = 4{\cdot}25$ and $c = 6{\cdot}69$ A., whereas in acetylenic soot the values are 4·21 and 7·1 A., respectively. The lattice is therefore deformed in soot, perhaps by residual hydrogen (usually about 1% by wt.) which is somehow attached and presumably located between the planes of the graphite. These planes still seem to be parallel in soot particles, as in graphite, but situated one on top of the other at random. Hofmann and Dietrich assume that the graphitising of any solid organic material such as a sugar at 1000° proceeds as follows: Nuclei of graphite are formed and the graphite crystallites grow from these nuclei by absorbing the surrounding material. The size of the final crystallite is given by the number of original nuclei. Below 1400° there is no further increase in size, but above that temperature aggregation occurs and the crystallites grow at the expense of each other. The last process is probably very slow and may not ordinarily occur to carbon particles in flames.

We believe that we may have observed a graphitising process of this kind in a liquid droplet during the pyrolysis of methane at high temperature. Liquid droplets in the mist which formed in the exit tube passed through the flame at the outlet and in doing so changed rapidly into a luminous streak and a soot particle. Complete vaporisation of the droplets probably did not occur.

The carbon particles which we collected from a non-smoky diffusion flame were approximately 100 A. in diameter and very uniform in size over the whole of the luminous zone. Although the particles are probably aggregates of small crystals, it seems fairly certain that they do not grow in the luminous zone in spite of the collisions which they undergo through Brownian motion. If these graphite particles do not grow after entering the luminous zone and their formation is through a graphitising process similar to that suggested by Hofmann and Dietrich, then the material from which they form must be of similar size, *viz.*, 100 A. Thus two possibilities arise: either (*a*) the material is all in the gas phase and the pregraphite particles are truly large molecules, or (*b*) the material is in the form of fine droplets which subsequently graphitise. Condensation of higher hydrocarbons of extremely low volatility may occur locally, even at elevated temperatures, if their saturation vapour pressure is reached.

An alternative explanation might be that some nuclei of carbon are formed spontaneously and that these grow by a surface reaction with the gaseous fuel molecules which come into contact with them. This is analogous with the way in which carbon is deposited on hot surfaces in contact with hydrocarbon gases, the carbon initially formed seeming to catalyse the reaction which leads to further deposition. Carbon formed in this way has a different structure, however, and is of a vitreous type with an *X*-ray pattern more closely resembling that of diamond. The structure of soot particles is definitely graphitic and this important difference seems to rule out this alternative mode of formation.

We may now consider whether the absorption experiments have any bearing on carbon

formation. We believe that they have, partly because a rapid spread of the absorption accompanied the onset of stronger luminosity in the diffusion flame at the outlet, and partly on account of the different behaviour of methyl alcohol. On pyrolysis methyl alcohol decomposed and formaldehyde was among the products, but the diffusion flame at the outlet remained non-luminous even at high temperature. No continuous absorption was observed comparable with that of the hydrocarbons. All lower hydrocarbons are transparent in the visible and ultra-violet regions and do not begin to absorb strongly above 2000 A. Recent data collected by Sponer and Teller (*Rev. Modern Physics*, 1941, **13**, 75) show that information about the gaseous state of higher hydrocarbons is very limited. Unsaturated 2 : 3-dimethylbut-2-ene shows the greatest shift in the ultra-violet region and absorption begins at 2300 A. With triple-bonded compounds the effect is more marked: acetylene has a banded spectrum reaching 2400 A. but a long optical path is necessary to observe it. The absorption of vinylacetylene (but-1-en-3-yne) reaches up to 2553 A. and is also banded. Aromatic compounds absorb strongly in the ultra-violet region but have characteristic bands. Similarly, poly-unsaturated compounds such as conjugated polyenes and the cyanine dyes have banded spectra. The bands progress from the ultra-violet towards the visible region as the number of double bonds increases, but even a mixture of such compounds would not show an absorption which could be mistaken for a continuum. In short it is impossible to relate the experimental results to existing data. It might be argued that the effect is caused by carbon particles or liquid droplets which absorb preferentially in the ultra-violet region. This, however, is very unlikely because the observed cut off is complete. Moreover, the absorption begins to spread at relatively low temperatures, at which the amount of carbon formed is negligible. We suggest that the absorption is due either to higher hydrocarbons in the gas phase which increase in molecular size as the temperature is raised, or to unstable intermediate compounds which have not been isolated. Small quantities of light oils are known to be produced during pyrolysis, this being direct evidence of the formation of higher hydrocarbons, but the possibility of an unstable intermediate cannot be eliminated. Unsaturated compounds, such as olefins and acetylene, which are present during the pyrolysis of any hydrocarbon may form temporary molecular associations under transient conditions. Moreover, an unstable intermediate might have continuous absorption because of the loose character of the bonds.

Tentatively we suggest that carbon formation in the flame occurs by one of the following two processes: (1) Higher hydrocarbons are formed by pyrolysis. The molecular weight and concentration of these increase until the saturation vapour pressure is exceeded, whereupon condensation occurs and fine droplets are formed. These droplets contain nuclei of graphite, and graphite crystallites grow in the manner described by Hofmann and Dietrich (*loc. cit.*) until each droplet is converted into carbon and hydrogen is largely eliminated. Since the droplets are moving in an increasing temperature gradient the process of graphitising must be more rapid than that of re-evaporation of the droplet.

(2) During pyrolysis of the hydrocarbon large unstable molecules are formed which tend to decompose again into their original material. If conditions are favourable, however, very large molecules may be formed which graphitise on entering a region of sufficiently high temperature. The graphitisation process is again similar to that proposed by Hofmann and Dietrich and depends on the spontaneous formation of carbon nuclei within the molecule. Each nucleus grows into a graphite crystallite until it meets the next crystallite growing from an adjacent nucleus inside the same molecule. The hydrogen atoms are freed and escape from the graphite structure.

Either process provides an explanation of the limited experimental evidence.

So far it has not been possible to offer any explanation of the results which were obtained with diffusion flames at low pressure, but these results will now be considered on the basis of the above theory. Data on pre-mixed flames indicate that each fuel molecule undergoes the same probable number of collisions to complete its reaction, whatever the total pressure. Similar data on diffusion flames are lacking, but it was found that at low pressures larger burners were again necessary and the flame was thereby enlarged. If the same processes are assumed to apply as in the pre-mixed flame, the decrease in the number of bimolecular collisions per second at the lower pressure is counterbalanced by the increased time available in the enlarged zone of the flame. Hence a low pressure limit seems unlikely for the diffusion flame as well as for the pre-mixed flame. Nothing in the experimental results contradicts this, as far as observations on the pale blue reaction zone is concerned, but there definitely is a marked decrease in carbon formation as indicated by the extinction of the luminous zone at low pressure. Now, if we assume that condensation of higher hydrocarbons precedes carbon formation, a low-pressure limit is readily explained since the partial pressure of these substances will eventually fall below

the saturation vapour pressure. If, however, we admit the existence of unstable intermediates which are supposed to be responsible for carbon formation, there must be a pressure limit at which the life time of the unstable molecule approaches the interval between collisions and the molecule has a greater chance of decomposing than of being built up by a subsequent collision. As the pressure is reduced, therefore, the formation of large unstable molecules and consequently of carbon would be retarded and eventually stopped.

Another observation, from the investigation of diffusion flames at reduced pressure, also seems capable of explanation in this way. The height of the diffusion flame should be independent of the pressure (for constant mass flow), but it was observed that the acetylene–air diffusion flame changed rather suddenly with pressure and the luminous zone opened out abruptly into an enlarged hollow cylinder (see Fig. 2*d*). Combustion below the strongly luminous rim takes place through interdiffusion of the acetylene molecules and the outside air or oxygen. This diffusion process is not seriously affected by the presence of bigger particles. Carbon dioxide, carbon monoxide, water, and other reaction products, which in a normal flame diffuse towards the centre, will be present in this enlarged flame. The acetylene molecules also diffuse freely and must have diffused away completely at a distance above the burner mouth equal to the height of a normal flame. If large fuel molecules have commenced to form low down they may be restricted from diffusing outside on account of the smaller diffusion coefficient relative to their size. Above the normal flame height, therefore, the central core of hot gases contains only carbon dioxide, carbon monoxide, water, and enlarged fuel molecules. The latter eventually lead to carbon formation.

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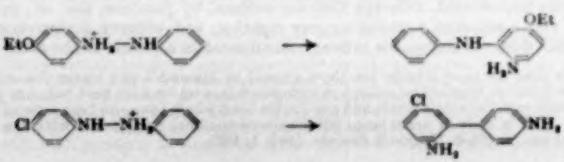
419. *The Stereochemistry of the Semidine Transformations.*

By D. LL. HAMMICK and D. C. MUNRO.

By postulating activated states similar to those put forward previously (Hammick and Mason, *J.*, 1946, 638) to explain the stereochemistry of the benzidine transformation, it is possible to show that during the conversion of hydrazobenzenes into either semidines or diphenylines, the reacting centres can be brought to "ionic-bond" length (*ca.* 2·5 A.) before rupture of the N—N link.

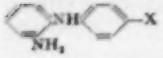
It is shown that for the *p*-semidine transformation the nearest approach is 4·9 A.; as, however, the direction of interchange of fragments during *p*-semidine transformation is opposite to that which takes place during the *o*-semidine change, it is concluded that the two changes are possibly not analogous. This view is supported by the fact that (i) all the recorded cases of the *p*-semidine transformation are brought about indirectly by the reduction of certain azo-compounds by using stannous chloride, (ii) reduction of such azo-compounds in the absence of metal ions yields no *p*-semidine but good yields of *o*-semidine.

THE *o*-semidine transformation of suitably substituted aromatic hydrazo-compounds is catalysed by all acids of sufficient strength. It is therefore reasonable to conclude that the transformation is, like the benzidine transformation (Hammick and Mason, *J.*, 1946, 638), a reaction of protonated hydrazines. The attachment of a single proton will be mainly to the more basic of the two imino-groups in the hydrazobenzene molecule, and it is possible to decide which is the more basic from the relative basicities of the corresponding substituted anilines ("fission bases"). It is found that with *para*-substituted hydrazobenzenes in which the *para*-substituted ring corresponds to the more basic aniline, semidines are formed. On the other hand, compounds, such as *p*-chloro- and *p*-bromo-hydrazobenzene, in which the *para*-substituted "fission base" is the less basic of the two give diphenylines. Thus:



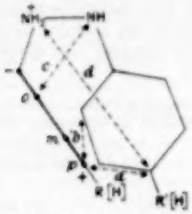
[The relevant basic constants are: *p*-phenetidine, $17{\cdot}9 \times 10^{-10}$; aniline, $3{\cdot}82 \times 10^{-10}$; *p*-chloroaniline, $0{\cdot}843 \times 10^{-10}$.]

The alternative *o*-semidine (shown inset) is apparently never formed (Jacobson, *Annalen*, 1922, **428**, 90—99, 106, 117).



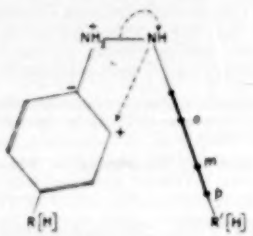
The intramolecular nature of the benzidine transformation of hydrazo-compounds must be regarded as established (Ingold and Kidd, *J.*, 1933, 984) and though there is no direct evidence in the case of the *o*-semidine transformation, the similarity between the conditions and results of the two processes makes it not unreasonable to suppose that both are intramolecular. The stereochemical implications of a continuous transition process in the case of the benzidine transformation have been discussed (Hammick and Mason, *loc. cit.*) in terms of the known bond lengths and interatomic distances. It was shown that in the various hybridised, semi-classical structures that can be written for the initial phase of the activated molecules undergoing the transformation, the *p*–*p*′ (and *p*–*o*′) positions come to within normal covalent bonding distances. The most significant of these structures is shown in Fig. 1.

Fig. 1.



(*a*) *Benzidine* 1·74 A.; (*b*) *diphenyline* 1·29 A.; (*c*) *o-semidine* 2·46 A. (*the value for the o-semidine change, is with the rings arranged as in Fig.* 2); (*d*) p-*semidine* 4·93 A.

Fig. 2.



It will be seen in Fig. 1 that the critical distance *c* for an *o*-semidine transformation is 2·46 A.,* which is of the order of an " ionic bond " in say a crystal of sodium chloride. Even if, therefore, during the passage through the transition state shown in Fig. 2, the positive charge at *o* in the left part is at a distance of about 2·5 A. from the negative nitrogen atom in the right part, the two fragments will be prevented from separating by the strength of an ionic bond.

The failure, in general, of hydrazo-compounds to give *o*-semidines when benzidines are possible, can be related to the greater energy required to set up the *o*-quinonoid resonance structures involved in the transition over that required for *p*-quinonoid structures. This mechanism is essentially a modification of that due to Robinson (*J.*, 1941, 220), and attempts to fulfil the stereochemical requirements of a continuous process, the aspect with which we are primarily concerned. Dewar (" Electronic Theory of Organic Chemistry," Oxford Univ. Press, 1949, pp. 233 *et seq.*) puts forward a mechanism which depends on the assumption of the primary dissociation of a hydrazo-molecule, such as hydrazobenzene, into aniline and a positive ion, $C_6H_5{\cdot}NH^+$. Cationoid attack by this ion on the aniline by the $-NH^+$ or by the *o*- and *p*-positive centres derived from it, lead to the known semidines, diphenylines, and benzidine derivatives. Separation of the cation and the aniline is prevented by π bonding. It is not immediately apparent how the π-bond formulation, in terms of a bond of indeterminate length and unknown strength, can provide a satisfactory way out of the stereochemical difficulties.

The relation of the *p*- to the *o*-semidine transformation presents problems which have not always been fully appreciated, although they are outlined by Jacobson (*loc. cit.*, pp. 106—117). In general, *p*- and *o*-semidine formation occur together, and without diphenyline formation; this suggests, but does not prove, the primary attachment of a proton to the same imino-group

* The values used for bond lengths are those quoted by Hammick and Mason (*loc. cit.*). All bond angles have been taken as tetrahedral, except in carbonium ions which have been taken as planar, and in quadrivalent atoms with two single bonds and one double bond which have also been taken as planar, with bonds at 120°. This is more in accordance with wave-mechanical results, and with the structures of benzene and ethylene (Coulson, *Quarterly Reviews*, 1947, **1**, 163).

in the formation of both semidines. But this is hard to reconcile with the fact that the *p*-semidine produced is derived, *e.g.*, in the case of *p*-ethoxyhydrazobenzene, by substitution of the phenetidine nitrogen into the aniline ring, whereas the *o*-semidine concurrently produced comes from the substitution of the aniline nitrogen into the phenetidine ring. This contrast is clear in Fig. 1, where R = OEt and R′ = H; the *o*-semidine union is *c*, whereas the *p*-semidine is *d*. It is to be noted that this distance in the activated state represented in Fig. 1 is 4·93 A., which is quite outside covalent- or ionic-bond length, and would imply ready fission.

A second important point in connection with the *p*-semidine transformation is that there is no recorded case of the change being brought about by the action of acid directly on a hydrazo-compound. In the 87 cases quoted by Jacobson (*loc. cit.*, pp. 90—99) all were carried out by the action of aqueous alcoholic stannous chloride and hydrochloric acid on azo-compounds. A single case (Barbier and Sisley, *Bull. Soc. chim.*, 1905, **33**, 1232) is recorded where zinc and sulphurous acid were substituted for stannous chloride. It thus becomes not only difficult to believe that the *p*-semidine transformation can be strictly analogous in mechanism to the other hydrazobenzene rearrangements, but it raises very definitely the question as to whether the presence of certain metallic ions is not crucial. We have attempted to effect a transformation by the action of hydrochloric acid on *p*-ethoxyhydrazobenzene, but the products were intractable. We have, however, found that when the reduction of appropriate azo-compounds is carried out in glacial acetic acid in the absence of metal ions, by the use of hydrogen and Raney nickel, no *p*-semidine is produced, but excellent yields of *o*-semidine are obtained. The case of 4-ethoxy-2′-methylazobenzene is particularly notable, because, when rearrangement is brought about by using stannous chloride in ethanol and hydrochloric acid, the main product is the *p*-semidine, and the separation of the small quantity of *o*-semidine is difficult (Jacobson, Franz, and Zaar, *Ber.*, 1903, **36**, 3860).

It is unprofitable to discuss mechanisms for the *p*-semidine transformation in terms of intermediate metallic complexes until more is known about its fundamental nature. There is as yet no direct evidence as to whether it is in fact intramolecular, or indeed whether it is a reaction of hydrazobenzenes at all. It appears to be certain that *p*-semidines cannot be produced by acids alone on hydrazobenzenes; moreover, under the conditions in which they are formed (reduction of azobenzenes in the presence of tin or zinc ions), considerable quantities of "fission bases" are also produced, and there is the possibility that *p*-semidines arise from catalysed interactions of Friedel–Crafts type.

Experimental.

The following 4-hydroxyazobenzene and corresponding compounds containing methyl groups were prepared by diazotisation and coupling by standard methods. The ethyl ethers were prepared by treatment of the hydroxy-compounds with sodium ethoxide and ethyl iodide, also by known methods: 4-hydroxyazobenzene, m. p. 152°, from ethanol; ethyl ether, m. p. 77°, from ethanol: 4-hydroxy-3-methylazobenzene, m. p. 128—129°, from ligroin; ethyl ether, m. p. 51°, from ethanol: 4-hydroxy-2′-methylazobenzene, m. p. 107°, from ethanol (Grandmougin and Freiman, *J. pr. Chem.*, 1908, **78**, 388, give m. p. 107—108°); m. p. 119°, from methanol or ligroin; ethyl ether, m. p. 51°, from ethanol; and 4-hydroxy-3 : 2′-dimethylazobenzene, m. p. 131°, from ethanol (Noelting and Werner, *Ber.*, 1890, **23**, 3259, give m. p. 132°), m. p. 148°, from methanol or ligroin; ethyl ether, m. p. 33°, from ligroin.

4-Aminoazobenzene. This was prepared by diazotisation of aniline and coupling of the product via diazoaminobenzene by standard methods; m. p. 122°, from ethanol.

Rearrangement experiments. Those by using stannous chloride were carried out more or less according to the methods described by Jacobson (*Annalen*, 1922, **428**, 85).

The ethoxy-azo-compound (1 g.) was dissolved in ethanol (20 c.c.) and a solution of stannous chloride (6 g.) in concentrated hydrochloric acid (20 c.c.) added. After ½ hour the mixture was made alkaline with 20% sodium hydroxide solution and filtered, and the residue dried and extracted with a mixture of toluene (1 part) and ligroin (3 parts). On cooling this solution, the *o*-semidine was usually obtained.

This method was used with some success on 4-ethoxyazobenzene and 4-ethoxy-3-methylazobenzene. The semidine from 4-ethoxy-3 : 2′-dimethylazobenzene was distilled at 2-mm. pressure in the absence of air.

The rearrangement of 4-ethoxy-2′-methylazobenzene was carried out as described by Jacobson, Franz, and Zaar (*loc. cit.*); it gave a yield of *o*-semidine corresponding to 3·5% of the original azo-compound.

Rearrangements by using the Raney nickel–acetic acid were carried out as follows. The azo-compound (2·0 g.) was dissolved in cold glacial acetic acid (30 c.c.) and Raney nickel (*ca.* 1 g.) added. Shaking the solution with hydrogen for five minutes ensured complete reduction, the actual decolorisation requiring only about two minutes. The catalyst was removed by filtration, water (100 c.c.) was added, and the bulk of the dilute acetic acid removed by distillation at 20-mm. pressure. The residue, after treatment with dilute sodium hydroxide solution, was extracted with ether, the extract dried (Na_2SO_4), and the ether removed. Two distillations under reduced pressure of the residue (without a leak which causes rapid oxidation) provided a separation from the lower-boiling fission bases (aniline, and

p-phenetidine and homologues). The *o*-semidines distilled at 160—190°/0·05 mm; the colourless to pale yellow distillate solidified slowly on cooling, and was recrystallised from *cyclo*hexane. Yields were normally 30—35%, the remainder of the azo-compound being converted into fission bases.

The *o*-semidines are white solids, generally crystalline. Aerial oxidation of the solid is slow, but that of solutions is rapid. They were characterised by their benzil derivatives:

2-Amino-5-ethoxydiphenylamine, m. p. 94—95° (Jacobson and Fischer, *Ber.*, 1892, **25**, 995, give m. p. 95°); benzil derivative, m. p. 162° (Jacobson, *Ber.*, 1892, **25**, 1010, gives m. p. 161—162°); 2-amino-5-ethoxy-4-methyldiphenylamine, m. p. 94°; benzil derivative, m. p. 139° (Jacobson, *Annalen*, 1895, **287**, 135, 147, gives m. p. 94—95 for the amine and m. p. 136° for the benzil derivative); 2-amino-5-ethoxy-2′-methyldiphenylamine, m. p. 83°; benzil derivative, m. p. 170° (Jacobson, Franz, and Zaar, *loc. cit.*, give m. p. 82—83° for the amine and m. p. 172° for the benzil derivative); 2-amino-5-ethoxy-4 : 2′-dimethyldiphenylamine, m. p. 77°; benzil derivative, m. p. 150—153° (Jacobson, *Annalen*, 1895, **287**, 190, gives m. p. 78° for the amine and m. p. 153° for the benzil derivative).

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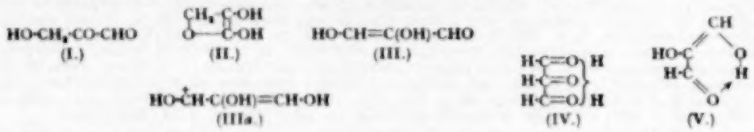
420. *The Chemistry of Reductone. Part II.* Some Condensation Products of Reductone with Amino-compounds.*

By WESLEY COCKER, R. A. Q. O'MEARA, J. C. P. SCHWARZ, and E. R. STUART.

Reductone has been condensed with various aromatic primary and secondary amines and certain α-amino-acids. The structures of these condensation products are discussed.

IN view of the biological significance of the condensation products of reductone with amino-compounds (Forrest and Walker, *J.*, 1949, 2002; Angier *et al.*, *J., Amer. Chem. Soc.*, 1948, **70**, 25; Bell, Cocker, and O'Meara, *Biochem. J.*, 1949, **45**, 373), it seemed desirable to investigate the formation and chemistry of these compounds in greater detail.

Although reductone can, theoretically, exist in a number of tautomeric modifications and a number of such structures have been suggested, *e.g.*, (I) (Norrish and Griffiths, *J.*, 1928, 2829), (II), (IV), and (V) (von Euler, Hasselquist, and Lööv, *Arkiv Kemi, Mineral., Geol.*, 1948, **26**, *A*, 17; von Euler and Hasselquist, *Arkiv Kemi, Mineral., Geol.*, 1949, **26**, *A*, 25), structure (III) (von Euler and Martius, *Annalen*, 1933, **505**, 73) seems to us, with our present information, to be the most acceptable. Incidentally, (V) is really the chelated *trans*-form of (III): molecular models show that chelation of the *cis*-form is stereochemically impossible.



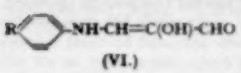
Reductone has been shown to condense, in the cold, with a number of amines, both in presence and in absence of mineral acid. Undoubtedly, in the latter conditions the yields and quality of products are inferior to those obtained when mineral acid is employed. This may be associated with the necessity for the opening of an acid-labile ring system such as (II), as suggested by von Euler, Hasselquist, and Lööv (*loc. cit.*), but it may be that the acid favours the formation of the reactive, symmetrical ion (IIIa).

The products obtained from reductone and aniline, *p*-chloroaniline, 2-naphthylamine, and sulphanilic acid are, respectively, **3**-anilino- (VI; R = H), **3**-*p*-chloroanilino- (VI; R = Cl), **3**-2′-naphthylamino- (VIa), and **3**-*p*-sulphoanilino-2-hydroxyprop-2-enal (VI; R = SO_3H). Compounds (VI; R = H and R = Cl) and (VIa) give the ene-diol colour reaction of Fearon and Kawerau (*Biochem. J.*, 1943 **37**, 326), but the reaction with (VI; R = SO_3H) was unsatisfactory. The compounds (VI; R = H) and (VIa) were shown to be completely enolic by titration with dichlorophenol-indophenol (Tillmans's reagent) in acid solution and this result was confirmed for (VI; R = H) by titration with iodine. Titration with iodine reveals that (VI; R = SO_3H) is only 50% enolic.

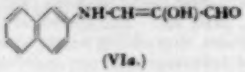
When reductone is condensed with methylaniline in presence of dilute acetic acid, **3**-*N*-methylanilino-2-hydroxyprop-2-enal (VII) is obtained. Although this compound does not

* The paper by Bell, Cocker, and O'Meara (*loc. cit.*) can be considered as Part I of this series.

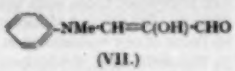
give Fearon and Kawerau's ene-diol reaction (*loc. cit.*) it can be quantitatively titrated with iodine or with Tillmans's reagent in acid solution. Oxidation of the groups $-C(OH)=C(OH)-$



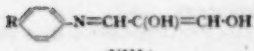
(VI.)



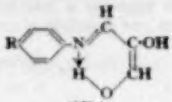
(VIa.)



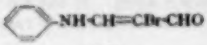
(VII.)



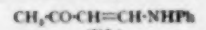
(VIII.)



(IX.)



(X.)

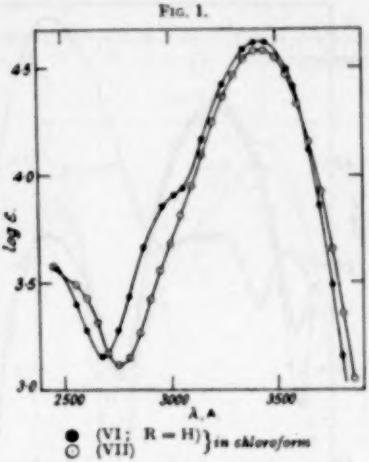


(XI.)

and $-C(OH)=C(NHR)-$ by *o*-dinitrobenzene would, on Fearon and Kawerau's view (*loc. cit.*), yield the systems $O=\dot{C}-\dot{C}=O$ and $O=\dot{C}-\dot{C}=NR$, but no such oxidation of $-C(OH)=C(NRR')-$ is possible; oxidation of the three enol systems with iodine or Tillmans's reagent, which proceeds in acid solution, may involve the production of $O=\dot{C}-\dot{C}=O$, $O=\dot{C}-\dot{C}=\overset{+}{N}R$, and $O=\dot{C}-\dot{C}=\overset{+}{N}RR'$ respectively, thus affording an explanation of the oxidation of $-C(OH)=C(NRR')-$, as in (VII), with iodine and Tillmans's reagent despite failure to react with *o*-dinitrobenzene.

The ultra-violet light absorption characteristics of a number of the amine and related condensation products are recorded in the Table and Fig. 1. The spectra of the condensation products of the primary amines are similar to that of the product from methylaniline and reductone which, if condensation is at an end carbon atom (see below), can only be of type (VII). The general structure (VI) has, therefore, been assigned to these products rather than (VIII) previously accepted by Angier *et al.* (*loc. cit.*) and by Bell, Cocker, and O'Meara (*loc. cit.*). It is clear, however, that in the chelated state (IX), the two forms of the primary amine derivatives become identical.

FIG. 1.



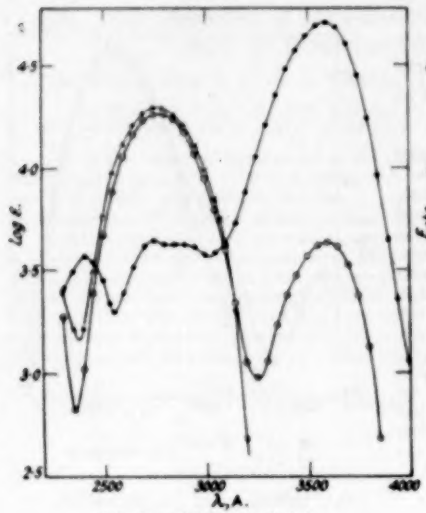
	In chloroform.		In ethanol.	
	$\lambda_{max.}$, A.	log $\varepsilon_{max.}$	$\lambda_{max.}$, A.	log $\varepsilon_{max.}$
$C_6H_5\cdot NH\cdot CH=C(OH)\cdot CHO$	3420	4·63	2320	3·74
			3420	4·58
$C_6H_5\cdot NMe\cdot CH=C(OH)\cdot CHO$	3420	4·59	2360	3·65
			3420	4·57
$C_6H_5\cdot NH\cdot CH=CBr\cdot CHO$	3230	4·61	—	—
$C_6H_4Cl\cdot NH\cdot CH=C(OH)\cdot CHO$	3460	4·68	—	—
$EtO_2C\cdot C_6H_4\cdot NH\cdot CH=C(OH)\cdot CHO$	2650	3·46	2420	3·57
	3570	4·82	2760	3·65
			3580	4·71
$BzO\cdot CH=C(OBz)\cdot CHO$	—	—	2370	4·46
			2540	4·47
$C_6H_5\cdot N=CH\cdot C(OH)=CH\cdot OBz$	—	—	(2920)	4·13
			3230	4·59
$C_6H_5\cdot NMe\cdot CH=C(OBz)\cdot CHO$	—	—	2310	4·29
			3050	4·48
$C_6H_5\cdot N=CH\cdot C(OBz)=CH\cdot OBz$	—	—	2290	4·42
			(2920)	4·04
			3250	4·47

We have examined the light absorption characteristics of 2-bromo-3-anilinoprop-2-enal (X) obtained from bromomalonaldehyde and aniline (Dieckmann and Platz, *Ber.*, 1904, **37**, 4637) and compared them with those of 1-anilinobut-1-en-3-one (XI) and related compounds (Bowden, Braude, Jones, and Weedon, *J.*, 1946, 45). The spectra of these compounds are very similar to those of our condensation products, thus adding weight to the view accepted by most workers in this field that condensation of reductone with one molecule of amine takes place at an end carbon atom. If the ion (IIIa) is taken as a reactive form of reductone in acid solution, a possible mechanism of reaction with one molecule of amine is as follows:

$$HO\text{-}\overset{\oplus}{C}H\text{-}C(OH)=CH\text{-}OH + Ph\text{-}NH_2 \longrightarrow Ph\text{-}\overset{\oplus}{N}H_2\text{-}CH(OH)\text{-}C(OH)=CH\text{-}OH \longrightarrow Ph\text{-}NH\text{-}CH=C(OH)\text{-}CHO + H^{\oplus} + H_2O$$

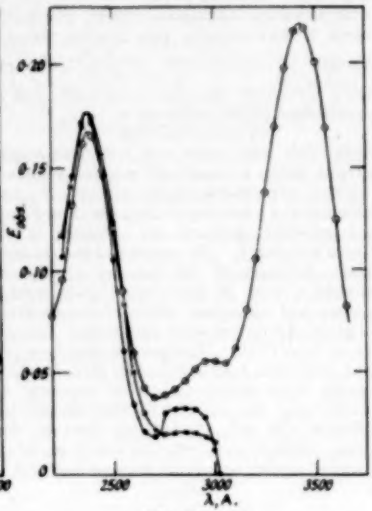
An interesting change in light-absorption characteristics took place, with time, in solutions of (VI; R = H, CO_2Et) in a large volume of alcohol (see Fig. 2*a*), but no similar change was

Fig. 2*a*.



(VI; R = CO_2Et) *in alcohol.*
● *after* 1 *hr.*
○ ,, 18 *hrs.*
× ,, 24 *hrs.*

Fig. 2*b*.



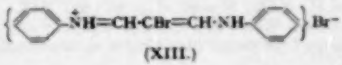
(VI; R = H.)
× "O_2" *alcohol* (4½ *hrs.*).
● "*Stock*" *alcohol* (24 *hrs.*).
○ "N_2" *alcohol* (24 *hrs.*).

observed in chloroform nor did alcoholic solutions of (VII) or of the dibenzoyl derivative (XVI) of reductone undergo any change. In the latter cases, the reducing system is, of course, blocked. The change is apparently associated with oxidation, since when (VI; R = H) was dissolved in alcohol, from which oxygen had been expelled by a current of nitrogen, the change in absorption characteristics was slowed and, on the contrary, the change was considerably accelerated when the solution was made up by using alcohol through which oxygen had been bubbled (Fig. 2*b*). The spectrum of the solution after a long period of time closely resembled that of formanilide, but attempts to isolate this compound from the oxidation of (VI; R = H) with alkaline or neutral hydrogen peroxide were unsuccessful, although a strong carbylamine odour was noted.

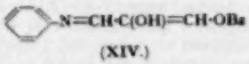
Compounds (VI; R = H) and (VII) give intense violet colours with ferric chloride. Concentrated sodium hydroxide converts them into their sodium salts which, when dried and shaken in dry ether with benzoyl chloride, yield 3-anilo-1-benzoyloxyprop-1-en-2-ol (XIV) and 3-*N*-methylanilino-2-benzoyloxyprop-2-enal (XV) respectively. The spectrum of (XIV)

differs from that of (XV) (Fig. 3), but resembles that of the condensation product of aniline with the dibenzoyl derivative (XVI; see below) of reductone; this product must obviously be (XVII). It is for this reason that we assign the structure (XIV) to the benzoylation product of (VI; R = H).

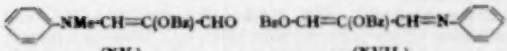
(XII.)



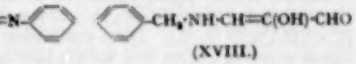
(XIII.)



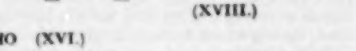
(XIV.)



(XV.)



(XVIII.)



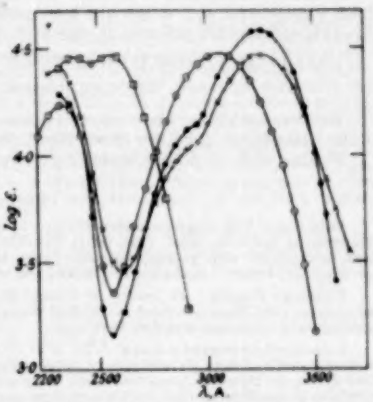
(XVII.)

(XVI.)

When (VI; R = H) is heated with aniline in dilute hydrochloric acid, it affords 3-anilino-1-aniloprop-2-en-2-ol hydrochloride (XII; R = H, R′ = H, X = Cl). This compound probably has the symmetrical resonance structure and this is supported by the fact that (XII; R = H, R′ = Cl, X = Cl) is obtained by condensation of (*a*) (VI; R = H) with *p*-chloroaniline or (*b*) (VI; R = Cl) with aniline (see below). The compound (XII; R = H, R′ = H, X = Cl) is also obtained when reductone is *heated* with one or two equivalents of aniline in the presence of hydrochloric acid or from (VI; R = H) by disproportionation with hydrochloric acid. 2-Bromo-3-anilinoprop-2-enal (X) disproportionates in a similar manner when heated with hydrobromic acid, giving 2-bromo-3-anilino-1-aniloprop-2-ene hydrobromide (XIII; Dieckmann and Platz, *loc. cit.*).

Von Euler, Hasselquist, and Lööv (*loc. cit.*) obtained a compound, m. p. 260°, by heating reductone with aniline in 4N-hydrochloric acid, which they considered to be the hydrochloride of a monoaniline derivative of reductone. They do not give an analysis of this compound, but base their structure solely on a titration of the crude material with Tillmans's reagent. Working under these conditions we obtained (XII; R = H, R′ = H, X = Cl) and this compound decolorised one mole (two atoms) of iodine per mole, and its titration with Tillmans's reagent agreed with this. We were also unable to obtain the "free base," m. p. 64° (again, no analyses were recorded), described by von Euler and his co-workers (*loc. cit.*). In our hands, basification of (XII; R = H, R′ = H, X = Cl) with alkali or sodium acetate gave a red precipitate which could not be purified; further, the odour of carbylamine was noticed.

FIG. 3.



● (XIV). ○ (XV). ⊡ (XVI). × (XVII).

Attempts to cyclise (VI; R = H) or (XII; R = H, R′ = H, X = Cl) to an indole or quinoline were unsuccessful. Concentrated sulphuric acid converted both compounds into (VI; R = SO_3H).

We have also obtained 3-*p*-toluidino-1-*p*-tolyliminoprop-2-en-2-ol hydrochloride (XII; R = Me, R′ = Me, X = Cl), 3-*p*-chloroanilino-1-*p*-chloroaniloprop-2-en-2-ol hydrochloride (XII; R = Cl, R′ = Cl, X = Cl), and 3-anilino-1-aniloprop-2-en-2-ol sulphate and acetate (XII; R = H, R′ = H, X = $\frac{1}{2}SO_4$ and OAc respectively) by condensation of the appropriate amine with reductone in presence of the appropriate hot dilute acid.

It is interesting that, when (VII) was heated with aniline in presence of hydrochloric acid, the methylaniline residue was eliminated and the dianilino-compound (XII; R = H, R′ = H, X = Cl) was obtained.

Benzylamine reacts with reductone in alcohol to give the benzylamine salt which is transformed, in aqueous solution on storage, into 3-benzylamino-2-hydroxyprop-2-enal (XVIII).

The dibenzoyl derivative of reductone (XVI) is obtained either from the dry sodium salt and benzoyl chloride in ether or by shaking reductone with benzoyl chloride in aqueous sodium acetate. The monobenzoyl derivative was not encountered.*

Reductone condenses readily with primary or secondary α-amino-acids in the presence or absence of hydrochloric acid. Except in the case of alanine, condensation products of the type (XIX) are produced, *e.g.*, from glycine, (±)-α-aminobutyric acid, and (±)-β-phenylalanine, we have obtained respectively (XIX; R = R′ = H: XIX; R = H, R′ = Et: and XIX; R = H, R′ = CH_2Ph). These compounds give Fearon and Kawerau's ene-diol test and are quantitatively oxidised by iodine and Tillmans's reagent. In water they titrate as monobasic acids; in alcohol, slightly higher figures are obtained.

N-Phenyl- and *N*-benzyl-glycine respectively yield (XIX; R = Ph, R′ = H; and R = CH_2Ph, R′ = H). These compounds titrate normally with iodine and Tillmans's reagent and as monobasic acids with sodium hydroxide, but the ene-diol colour only appears after some time, during which hydrolysis probably occurs.

(±)-Alanine reacts abnormally with reductone yielding a compound which analyses as $C_9H_{11}O_4N$ or $C_9H_{13}O_4N$. This compound is not oxidised by iodine or Tillmans's reagent, nor does it give the ene-diol reaction. It titrates as a dibasic acid and gives a powerful red-brown ferric reaction. Structure (XX) or (XXI) seems likely for this compound. However, attempts to condense reductone with αα′-iminodipropionic acid, which could afford (XXI), have so far been unsuccessful and it has not been possible to condense (XIX; R = R′ = H) or (VI; R = H) with another molecule of reductone.

(XIX.) OHC·C(OH)=CH·NR·CHR′·CO_2H [OHC·C(OH)=CH_2N·CHMe·CO_2H (XX.)

OHC·C(OH)=CH·N(CHMe·CO_2H)$_2$ (XXI.)

We were unable to obtain a product from (−)-L-leucine and reductone as described by von Euler, Hasselquist, and Lööv (*Arkiv Kemi, Mineral., Geol.*, 1948, **26**, *A*, 17).

Further work on the condensation of reductone with amino-acids is in progress.

Experimental.

Reductone.—This compound was obtained by a modification of the method described by von Euler, Hasselquist, and Lööv (*ibid.*, 1948, **26**, *B*, 5). The dried lead salt of reductone was suspended in acetone and decomposed with phosphoric acid. After filtration the solution was concentrated under reduced pressure and cooled. Reductone separated and was washed with a little acetone.

Tillmans's Reagent.—10 Tablets of dichlorophenol-indophenol (B.D.H.; each tablet equiv. to 1 mg. of ascorbic acid) were dissolved in distilled water (50 c.c.) giving a 0·00227*N*-solution. Titrations were carried out in presence of hydrochloric acid.

3-*Anilino*-2-*hydroxyprop*-2-*enal* (VI; R = H).—A mixture of reductone (0·5 g.), aniline (0·5 c.c.), concentrated hydrochloric acid (0·5 c.c.) and water (7 c.c.) was set aside at 0° for 2 hours and the product (0·7 g.; m. p. 116—118°) was collected. The *aldehyde* was obtained as colourless needles, m. p. 118—120°, by crystallisation from chloroform–light petroleum (Found: C, 66·3; H, 5·5; N, 7·8. $C_9H_9O_2N$ requires C, 66·2; H, 5·5; N, 8·6%). The same product was obtained (0·5 g.; m. p. 95—96°) when a mixture of reductone (0·5 g.), aniline (0·5 c.c.) in alcohol (1·5 c.c.) and water (30 c.c.) was shaken for 2 hours. The compound (1·26 mg.) in acidified alcohol required 6·4 c.c. of Tillmans's reagent (2 equivs. require 6·8 c.c.). The compound (15·3 mg.) required 18·6 c.c. of *N*/100-iodine, benzene being used as indicator (2 equivs. require 18·8 c.c.).

3-p-*Chloroanilino*-2-*hydroxyprop*-2-*enal* (VI; R = Cl) was obtained (0·95 g.) when a mixture of reductone (0·5 g.), *p*-chloroaniline (0·7 g.), concentrated hydrochloric acid (1 c.c.) and water (10 c.c.) was kept at 0° for 2 hours. The *aldehyde* crystallised from very dilute alcohol (charcoal) as pale yellow needles, m. p. 168—170° (Found: C, 54·8; H, 4·3; N, 6·8. $C_9H_8O_2NCl$ requires C, 54·7; H, 4·1; N, 7·1%).

3-(2-*Naphthylamino*)-2-*hydroxyprop*-2-*enal* (VIa) was obtained (0·8 g., m. p. 145—150°) from reductone (0·5 g.) as described for the above compounds. It crystallised from chloroform as golden plates, m. p. 151—152° after shrinking at 145° (Found: C, 72·7; H, 5·0; N, 6·4. $C_{13}H_{11}O_2N$ requires C, 73·2; H, 5·2; N, 6·6%).

3-(p-*Sulphoanilino*)-2-*hydroxyprop*-2-*enal* (VI; R = SO_3H), obtained by warming equivalent quantities of reductone and sulphanilic acid in water, crystallised from water as yellow small needles, m. p. 298° (decomp.) (Found: C, 41·2; H, 4·2; N, 5·4; S, 12·6. $C_9H_9O_5NS,H_2O$ requires C, 41·4; H, 4·2; N, 5·4; S, 12·3%).

* [*Added, May 4th, 1950.*] Since this paper was submitted, the monobenzoyl derivative of reductone has been obtained by shaking the sodium salt of reductone with benzoyl chloride in dry benzene. Details will be published later.

The same compound was obtained when (VI; R = H) (0·2 g.) was treated with concentrated sulphuric acid (*a*) in the cold for 2 hours or (*b*) at 100° for 15 minutes. Pouring the solutions into water gave (VI; R = SO_3H).

3-N-*Methylanilino*-2-*hydroxyprop*-2-*enal* (VII).—A mixture of reductone (1 g.), methylaniline (1 c.c.), acetic acid (4 c.c.) and water (9 c.c.) was kept at 0° for 5 days. The *aldehyde* (0·7 g.; m. p. 100—103°) crystallised from dilute alcohol as colourless plates, m. p. 106—107° (Found: C, 68·3; H, 6·5; N, 7·9. $C_{10}H_{11}O_2N$ requires C, 67·8; H, 6·2; N, 7·9%). 1·97 Mg., titrated in alcohol containing hydrochloric acid, required 10 c.c. of Tillmans's reagent (2 equivs. require 9·8 c.c.).

Benzylamine Salt of Reductone.—The *salt* separated when benzylamine (0·22 c.c.) was added to reductone (0·2 g.) in alcohol (4 c.c.), as plates, m. p. 77—79° (Found: C, 61·6; H, 6·3; N, 7·3. $C_7H_9N,C_3H_4O_3$ requires C, 61·5; H, 6·7; N, 7·2%). Its solution in water gradually deposited a solid, m. p. 70—90°, which could not be crystallised. This is probably 3-*benzylamino*-2-*hydroxyprop*-2-*enal* (XVIII) (Found: C, 64·3; H, 6·0. $C_{10}H_{11}O_2N,\frac{1}{2}H_2O$ requires C, 64·5; H, 6·5%).

3-*Anilo*-1-*benzoyloxyprop*-1-*en*-2-*ol* (XIV).—The substance (VI; R = H), dissolved in a minimum quantity of alcohol, was treated with excess of sodium hydroxide (25%). The precipitated sodium salt was collected, washed with alcohol, and dried with ether. The finely powdered salt (0·85 g.) was suspended in ether (20 c.c.), shaken with benzoyl chloride (0·34 c.c.) for 18 hours and then with sodium hydrogen carbonate solution, and filtered. The pale yellow *residue* (0·2 g.; m. p. 156—158°) crystallised from benzene as colourless prisms, m. p. 157—158° (Found: C, 72·9; H, 5·1; N, 4·9%; *M*, 247. $C_{16}H_{13}O_2N$ requires C, 71·9; H, 4·9; N, 5·2%; *M*, 267). It gave a reddish-brown colour with ferric chloride.

3-N-*Methylanilino*-2-*benzoyloxyprop*-2-*enal* (XV), similarly obtained from (VII) in 70% yield, crystallised from dilute alcohol as pale yellow prisms, m. p. 151° (Found: C, 72·2; H, 5·5; N, 4·3. $C_{17}H_{15}O_3N$ requires C, 72·6; H, 5·3; N, 5·0%).

3-*Anilino*-1-*anilopropa*-2-*en*-2-*ol Hydrochloride* (XII; R = H, R′ = H, X = Cl), *etc.*—A mixture of reductone (1 g.), aniline (2 c.c.), hydrochloric acid (3·4 c.c.), and water (10 c.c.) was heated at 65° for 10 minutes. On cooling, the *hydrochloride* (1·5 g.) was deposited and crystallised from dilute alcohol as golden yellow needles, m. p. 245—255° (decomp.) according to the rate of heating (Found: C, 65·6; H, 5·6; N, 9·5. $C_{15}H_{14}ON_2HCl$ requires C, 65·6; H, 5·5; N, 10·2%). The same compound was obtained when (VI; R = H) (0·5 g.) was heated with hydrochloric acid (2 c.c.) and water (3 c.c.) for 10 minutes on the water-bath. The corresponding *sulphate* was obtained when the reaction was performed in sulphuric acid (*ca.* 15%). It crystallised from dilute alcohol as yellow needles, m. p. 203—208° (decomp.) [Found: C, 59·2; H, 5·7; N, 9·4. $(C_{15}H_{14}ON_2)_2,H_2SO_4,2H_2O$ requires C, 59·0; H, 5·6; N, 9·2%]. The *acetate* was obtained when reductone (0·5 g.), aniline (1 c.c.), water (9 c.c.), and acetic acid (5 c.c.) were heated gently for 5 minutes; it crystallised from chloroform as yellow needles, m. p. 150—153° (Found: C, 63·5; H, 5·9; N, 7·9; $CH_3{\cdot}CO_2H$, 34·4. $C_{15}H_{14}ON_2,2C_2H_4O_2$ requires C, 63·7; H, 6·1; N, 7·8; $CH_3{\cdot}CO_2H$, 33·8%).

3-p-*Toluidino*-1-p-*tolyliminoprop*-2-*en*-2-*ol Hydrochlorides* (XII; R = Me, R′ = Me, X = Cl), prepared in a similar manner to the aniline analogue, crystallised from dilute alcohol as yellow needles, m. p. 264° (decomp.) (Found: C, 67·5; H, 6·1; N, 9·0. $C_{17}H_{18}ON_2HCl$ requires C, 67·4; H, 6·3; N, 9·3%).

3-p-*Chloroanilino*-1-p-*chloroanilopropa*-2-*en*-2-*ol hydrochloride* (XII; R = Cl, R′ = Cl, X = Cl) crystallised from glacial acetic acid as yellow needles, m. p. 274—276° (decomp.) (Found: C, 52·5; H, 4·1; N, 8·4. $C_{15}H_{11}ON_2Cl_3HCl$ requires C, 52·4; H, 3·8; N, 8·2%).

3-p-*Chloroanilino*-1-*anilopropa*-2-*en*-2-*ol hydrochloride* (XII; R = H; R_1 = Cl; X′ = Cl) was obtained when (VI; R = Cl) (0·6 g.) in alcohol (15 c.c.) was heated with aniline hydrochloride (0·5 g.) and concentrated hydrochloric acid (1 c.c.) for 5 minutes on the water-bath. It crystallised from a large volume of alcohol as golden-yellow prisms, m. p. 262—265° (decomp.) (Found: C, 57·4; H, 4·2; N, 8·9. $C_{15}H_{11}ON_2Cl,HCl$ requires C, 58·3; H, 4·3; N, 9·1%). The same compound is obtained when (VI); R = H is heated with *p*-chloroaniline hydrochloride.

2 : 3-*Dibenzoyloxyprop*-2-*enal* (XVI).—The sodium salt of reductone (von Euler, Hasselquist, and Lööv, *Arkiv Kemi, Mineral., Geol.*, 1948, **26**, *B*, 8), finely powdered (3·7 g.), benzoyl chloride (3·6 c.c.), and ether (70 c.c.) were shaken for 10 hours. After being shaken with water and sodium hydrogen carbonate solution, the mixture was filtered. The residue crystallised from alcohol as needles, m. p. 115—125° (Found: C, 69·1; H, 4·3%; *M*, 314. $C_{17}H_{12}O_5$ requires C, 68·9; H, 4·1%; *M*, 296). It gave no ferric reaction.

2 : 3-*Dibenzoyloxyprop*-2-*enylideneaniline* (XVII).—This *anil* was obtained when the previous compound (XVI) (0·5 g.) in benzene (6 c.c.) was warmed gently for 3 minutes with aniline (0·16 c.c.). It separated on cooling and crystallised from benzene as yellow needles, m. p. 126—128° (Found: C, 74·0; H, 5·3; N, 3·1. $C_{23}H_{17}O_4N$ requires C, 74·4; H, 4·6; N, 3·8%). It gave no ferric reaction.

When (VII) (0·54 g.) was heated in water (6 c.c.) with hydrochloric acid (1 c.c.) and aniline hydrochloride (0·42 g.) for 5 minutes on the water-bath, it yielded (XII; R = H, R′ = H, X = Cl) (Found: C, 65·7; H, 5·3%).

Condensation of Reductone with α-Amino-acids.—(a) *With glycine.* A mixture of reductone (0·8 g.), glycine (0·5 g.), N-hydrochloric acid (1 c.c.), and water (4 c.c.) was heated in the water-bath for 3 minutes. On cooling, the N-(2-*hydroxy*-2-*formylvinyl*)*glycine* (XIX; R = R′ = H) (0·3 g.) was deposited. It crystallised from water as colourless prisms, m. p. 171—173° (decomp.) (Found: C, 41·8; H, 5·3; N, 9·0. $C_5H_7O_4N$ requires C, 41·4; H, 4·8; N, 9·8%).

(b) *With* (±)-*α-aminobutyric acid.* α-N-(2-*Hydroxy-2-formylvinyl*)*aminobutyric acid* (XIX; R = H, R′ = Et) crystallised from water as prisms, m. p. 171° (decomp.) (Found: C, 48·6; H, 6·0; N, 8·2. $C_8H_{11}O_4N$ requires C, 48·6; H, 6·4; N, 8·1%). During the preparation of this compound, the odour of propaldehyde was noticed; no doubt this arose from the oxidation of the amino-acid by an oxidised form of reductone (cf. Schönberg, Moubasher, and Mostafa, *J.*, 1948, 176).

(c) *With* (±)-*β-phenylalanine.* This condensation, with reductone (0·5 g.), was performed in more dilute solution (15 c.c. of water) and heating was extended to 10 minutes. α-N-(2-*Hydroxy-2-formylvinyl*)*amino-β-phenylpropionic acid* (XIX; R = H, R′ = CH_2Ph) (0·6 g.) crystallised from water as prisms, m. p. 181° (decomp.) (Found: C, 61·1; H, 5·0; N, 6·1. $C_{12}H_{13}O_4N$ requires C, 61·3; H, 5·5; N, 6·0%).

(d) *With* N-*phenylglycine.* The condensation, performed as in (a), gave N-*phenyl*-N-(2-*hydroxy-2-formylvinyl*)*glycine* (XIX; R = Ph, R′ = H), first as an oil; this solidified to a yellow solid (1·0 g. from 0·6 g. of reductone) and crystallised from water as pale orange prisms, m. p. 137—138° (Found: C, 59·6; H, 4·9; N, 6·6. $C_{11}H_{11}O_4N$ requires C, 59·7; H, 5·0; N, 6·3%).

(e) *With* N-*benzylglycine.* From reductone (0·6 g.), N-*benzyl*-N-(2-*hydroxy-2-formylvinyl*)*glycine* (XIX; R = CH_2Ph, R′ = H) (0·5 g.) was obtained, which crystallised from 50% alcohol as colourless rhombs, m. p. 159° (decomp.) (Found: C, 61·6; H, 5·3. $C_{12}H_{13}O_4N$ requires C, 61·3; H, 5·5%).

(f) *With* (±)-*alanine.* The requisite conditions in this case seem to be more specific. Reductone (0·5 g.) and α-alanine (0·5 g.) in water (4 c.c.) containing N-hydrochloric acid (1 c.c.) were heated on the water-bath for 10 minutes. On cooling and scratching, the *product*, probably (XX) or (XXI) (0·1 g.), separated. It crystallised from water as pale yellow rhombs, m. p. 220° (decomp.) (Found: C, 47·5; H, 4·1; N, 6·4. $C_8H_{11}O_4N$ requires C, 48·8; H, 5·6; N, 6·1. $C_7H_{11}O_4N$ requires C, 47·2; H, 4·8; N, 6·1%).

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421. *Separation of Lanthanons by Means of Complexes with Amino-acids.*

By R. C. VICKERY.

The formation of complexes by amino-acids with the lanthanons affords an effective method of separating the lighter earths by oxalate fractionation but has little effect on the heavy lanthanons. Of the amino-acids studied, histidine forms the strongest complexes, glycine being less efficient; other amino-acids are of but little value. Rapid separation of lanthanum is obtained, as well as speedy concentration of samarium; some separation of praseodymium and neodymium is also observed. Indications have been found of the possible existence of two stages of co-ordination with the amino-acids, and some crystalline lanthanon–amino-acid complexes have been prepared and analysed.

RECENT developments in the chemical separation of the lanthanons depend upon the use of agents forming complexes of varying stability with these elements. Prandtl (*Z. anorg. Chem.*, 1922, **120**, 120, etc.) early showed the value of ammine groupings in lanthanon separations; Beck (*Helv. Chim. Acta*, 1946, **29**, 357) has utilised nitrilotriacetate complexes, and the author (*J.*, 1950, 1101) recently indicated the use of carboxylic as well as amino-groups in double sulphate fractionation. Marsh (*J.*, 1950, **1819**) has since demonstrated the value of ethylenediamine-*NNN′N′*-tetra-acetic acid as co-ordinating agent in separations of both light and heavy lanthanon groups.

Schwarzenbach and his school (*Helv. Chim. Acta*, 1945, **28**, *et seq.*) found that ethylenediaminetetra-acetic acid and 1:2-diaminocyclohexane-*NNN′N′*-tetra-acetic acid were the strongest co-ordinating agents for the alkaline earths and that the co-ordinating strengths of these agents held also for certain of the tervalent elements including lanthanum and cerium.

The structures necessary for formation of complexes of this type are summarized by Marsh (*loc. cit.*) as " one or more secondary or tertiary amino-groups, and two or more acetate radicals so disposed as to give rise to chelate structures." It would be expected therefore that the amino-acids might prove of value in the formation of complexes with the lanthanons. The co-ordinated compound of copper with glycine is well known and presents many analogies to that with ethylenediamine, so lanthanon–amino-acid compounds should show many features comparable with those of the ethylenediamine compounds and thus be useful for fractionation.

It might, moreover, be expected that the amino-acids should be of two-fold value, their " zwitterionic " characteristics rendering chelation possible at both ends of the molecule.

Ryabchikov and Terent'eva (*Izvest. Akad. Nauk. S.S.S.R., Otdel Khim. Nauk.*, **1949**, 44) indicated that, of the amino-acids, glutamic and aspartic acids form the most stable complexes with lanthanons, and Pfeiffer (*Annalen*, **1933**, **503**, 84; *J. pr. Chem.*, **1933**, **136**, 321) showed that of the amino-acids, $NH_2 \cdot [CH_2]_n \cdot CO_2H$, those with $n = 1$ or 2, giving rise to 5- or 6-membered rings respectively, alone function as chelating groups.

According to Schmidt and Smythe (*J. Biol. Chem.*, 1930, **88**, 241) complexes should best be formed by amino-acids possessing a hydroxyl group in the α-position with respect to the carboxyl group and by the dicarboxylic amino-acids providing that no CH_2 groups interpose between the carboxyl groupings. It would be difficult to adhere to these criteria but it might reasonably be expected that co-ordination would be more likely the higher the concentrations of amino- and carboxylic groupings. The stability of the complex formed with cystine, however, is not so high as that with glycine, probably owing to the sulphur atoms present in the molecule.

Comparative stability constants have been given by Maley and Mellor (*Nature*, **1948**, **161**, 437; 1950, **165**, 453; *Australian J. Sci. Res.*, **1949**, *A*, **2**, 92) for ethylenediamine and amino-acid complexes of bivalent metal ions; Schwarzenbach (*loc. cit.*) gives p*K* values of 9·8 and 9·2 for lanthanum and cerium ethylenediamine compounds, respectively, and in this region the constants for histidine and ethylenediamine are quite comparable. Histidine apparently forms complexes more readily than do the other amino-acids, and Maley and Mellor suggest that this may be due to attachment by amino- and imino-groupings rather than the amino- and carboxyl groupings of other amino-acids—this is more or less confirmation of the assumption (see above) that it is the constitutional concentration of amino-groups which influences the co-ordinating strength. Apart from the degree of attachment of the co-ordinating group there is good reason to assume that basicity has much to do with the stability of individual lanthanon complexes—this is also indirectly stated by Irving and Williams (*Nature*, **1948**, **162**, 746): " the more stable the complex the lower the pH at which it can exist."

The use of amino-acids for forming complexes with the lanthanons appears confined from the practical aspect to glycine and histidine. Glutamic and aspartic acids and cystine, although apparently forming complexes to a small degree, are ineffective in aiding separation of the lanthanons—in this respect it has not been possible to confirm the Russian workers' results (*loc. cit.*) that glutamic and aspartic acids form the most stable complexes. Of all the amino-acids studied, histidine and glycine are the only ones to co-ordinate with lanthanon hydroxides in neutral or ammoniacal solutions. Ammoniacal solutions of the other amino-acids will not form complexes at all and require acidification in order to obtain solution. From these acid solutions only oxalate precipitation is practicable, and except with histidine and glycine separation was normally little better than ordinary oxalate precipitation, the lanthanum coming out at the tail in small yield but of good purity.

It would, however, appear that two types of co-ordination exist between the lanthanons and the amino-acids. If excess of lanthanon hydroxides is digested with aqueous glycine or histidine, and the solution filtered from excess of hydroxide, the lanthanon solution, on fractional precipitation with oxalic acid, separates in the normal sequence, *i.e.*, in inverse order of atomic number although with a somewhat enhanced separation. If, however, appreciable excess of amino-acid is employed for complete dissolution of the lanthanon hydroxides, then fractional oxalate precipitation will bring down the lanthanum at the head with the other earths following in order of atomic number, giving a degree of separation equivalent to that obtained by Marsh with ethylenediaminetetra-acetate. There thus appears to be a primary solvation effect with but little co-ordination, and a secondary fully co-ordinating effect. Possibly there exists an equilibrium in the first effect which depresses full co-ordination and this equilibrium is destroyed by the presence of excess of amino-acid. Since this effect has been noted with both glycine and histidine complexes, it cannot be ascribed to an antagonism between amino- and imino-groupings for complex-formation but might be a more general effect for hydroxides of high basicity, indicating antagonism between carboxyl and amino-groupings.

Such a hypothesis would explain the discrepancy of the degree of co-ordination found here with that given by the Russians, for if they obtained only the primary complex in some cases and full co-ordination in others, then their observations on the comparative stability of such complexes would be invalid.

Reversal of the oxalate series is in line with that obtained with ethylenediaminetetra-acetate and is probably indicative of full co-ordination.

With histidine as co-ordinating agent, fractional precipitation with oxalic acid enables good concentrations of lanthanum and samarium to be obtained at the head and tail of a short series. Table II shows that lanthanum increased from 40 to 95% in the first fraction and was absent after

the fourth: in six fractions samarium was increased from 5·0 to 50%; some separation of praseodymium and neodymium is also seen. Fractionation in the presence of glycine is not so effective (see Table I); increase of the number of fractions to eight gave a 90% lanthanum at the head with only the last two fractions free from this element (determined by spark spectroscopy); a 40% samarium concentrate was obtained at the tail but praseodymium and neodymium showed little separation.

Co-ordination should be greater with the heavy, less basic lanthanons, but very little separation could be obtained in this group in the presence of either histidine or glycine. Extension of the series to eighteen fractions gave a certain removal of erbium from the first half of the series, but apart from this negligible variations were obtained.

Fractionation as oxalates in the presence of histidine is probably as effective as with ethylenediaminetetra-acetic acid; amino-acids, however, cannot directly form complexes again with the precipitated oxalates, so continued fractionation by this means requires intermediate conversion into hydroxides before a series can be carried on. Nevertheless, the effectiveness of the method here described is further indication of the greatly enhanced separations obtained by the use of co-ordinating agents.

Experimental.

Preliminary qualitative work showed that of all the amino-acids only aqueous solutions of histidine and glycine would form complexes with lanthanon hydroxides in neutral or ammoniacal solutions. In acid solutions all the amino-acids formed complexes but in such cases it was difficult to determine which had most effect, solvating action of the mineral acid or co-ordinating action of the amino-acid. Quantitative work was therefore only carried out with histidine and glycine.

Glycine Complexes: Separation of the Light Lanthanons.—The lanthanon hydroxides were derived from mixed sources but were approximately in the same ratio as in monazite minus cerium. 75 G. of hydroxide (65 g. of oxide) were treated with 440 ml. of 20% aqueous glycine with slight warming to give a faintly turbid solution. The turbidity could be cleared with one or two drops of hydrochloric acid but this addition appeared to alter the structure of crystals obtained from the solution. The neutral solution crystallised quite well, giving hexagonal, wurtzite-type crystals; the acidified solution yielded, however, well-formed octahedra.

After dissolution of the hydroxides a further 450 ml. of glycine solution were added to ensure complete co-ordination. The lanthanons were then fractionally precipitated from the solution at 80—90° by appropriate quantities of 10% aqueous oxalic acid. The final fraction was always formed slowly and required the addition of a few drops of ammonia solution to initiate precipitation. Individual fractions were filtered off, ignited to oxide, redissolved in acid, and their compositions determined, in some cases by spectrophotometric means, but in the majority of cases by visual, and spark, spectroscopy in comparison with standards, and absorptiometrically on the "Spekker" instrument. The results obtained are shown in Table I. Table Ia shows data obtained when insufficient complex was formed by the

Table I.

Co-ordination with glycine.

Fraction no.	La, %	Pr, %	Nd, %	Sm, %	Fractional wts.	Fraction no.	La, %	Pr, %	Nd, %	Sm, %	Fractional wts.
0	40	12·5	42·0	5·0	100	5	5	27	62	4	9
1	95	—	—	—	22	6	2	18	58	10	10
2	50	13	22	—	10	7	—	15	57	20	12
3	30	20	25	—	17	8	—	2	52	40	10
4	15	25	47	—	10						

Table Ia.

Partial co-ordination with glycine.

Fraction no.	La, %	Pr, %	Nd, %	Sm, %	Fraction no.	La, %	Pr, %	Nd, %	Sm, %
2	10	15	35	38	7	40	10	30	13
4	30	18	35	13	8	55	5	15	22

employment of excess of hydroxide. The reversal of the series is well shown; the values for samarium in the final fraction might be considered anomalous and due to the fact that the solution employed for spectrophotometry had a green tinge, possibly due to unknown impurities. On the other hand, it might be considered that with the partial removal of lanthanons from the system by precipitation, the liberated glycine sufficed to form complexes with all the residual earths, with the result that partial reversal of the fractionation was exhibited towards the tail of the series. The separation achieved in fully co-ordinated solution is reasonably good with respect to samarium and lanthanum; neodymium and praseodymium appear to split to a small degree but this effect is not noteworthy.

Octahedra from the faintly acid solution crystallise well, and the *lanthanum* complex was analysed [Found: La_2O_3, 45·0; $(NH_2{\cdot}CH_2{\cdot}CO_2)$, 61·1. $La(NH_2{\cdot}CH_2{\cdot}CO_2)_3$ requires La_2O_3, 45·2; $(NH_2{\cdot}CH_2{\cdot}CO_2)$, 61·3%].

Histidine Complexes.—Prepared similarly to the glycine complexes, those of the light earths, upon oxalate fractionation, yielded the results given in Table II. A much better separation of samarium and lanthanum is obvious and a fair degree of neodymium/praseodymium separation is evident.

TABLE II.

Co-ordination with histidine.

Fraction no.	La, %	Pr, %	Nd, %	Sm, %	Fractional wts.	Fraction no.	La, %	Pr, %	Nd, %	Sm, %	Fractional wts.
0	40	12·5	42·0	5·0	100	4	2	15	80	3	16
1	95	—	—	—	25	5	—	8	67	10	15
2	45	18	28	—	20	6	—	4	50	50	8
3	25	35	56	2	16						

The initial lanthanon–histidine solution was quite clear (contrast the glycine complex) and yielded flat monoclinic crystals [Found: Ln_2O_3, 28·0 (average atomic weight of lanthanon 142); C, 30·1; N, 21·2. Calc. for $Ln(C_6H_9O_2N_3)_3$: Ln_2O_3, 27·8; C, 35·8; N, 20·9%].

Fractionation of a heavy lanthanon mixture of average atomic weight 115 did not yield very successful results. Solution was easily obtained but oxalate fractionation, even when extended to 18 fractions, gave only a mediocre separation—the head fraction of average atomic weight 98, and the tail of 122. Visual spectroscopy showed erbium to be less in the first eight fractions than subsequently.

Complexes with Other Amino-acids.—Although not employed for separations, co-ordination compounds of lanthanon with cystine, glutamic acid, and aspartic acid were prepared in solutions containing a trace of chloride and crystallised until free from chloride. The compound with cystine formed monoclinic rosettes [Found: Ln_2O_3, 33·0; S, 19·0; C, 21·0; N, 8·0. Calc. for $Ln_2(C_6H_{12}O_4N_2S_2)_3$: Ln_2O_3, 32·8; S, 19·0; C, 21·4; N, 8·3%]; that with glutamic acid formed rhombic platelets [Found: Ln_2O_3, 46·6; C, 24·6; H, 3·05; N, 5·5. Calc. for $Ln_2(C_5H_7O_4N)_3$: Ln_2O_3, 46·2; C, 25·0; H, 2·9; N, 5·85%]; and that with aspartic acid, monoclinic prisms [Found: Ln_2O_3, 49·6; C, 21·5; H, 2·0; N, 6·0. Calc. for $Ln_2(C_4H_4O_4N)_3$: Ln_2O_3, 49·0; C, 21·3; H, 2·2; N, 6·2%].

The author thanks Mrs. J. Wolfendale and Mr. J. Dobs for carrying out several of the analyses, and Dr. J. K. Marsh for spectrophotometric readings and helpful criticism.

1, SPRULES ROAD, BROCKLEY, S.E.4. [*Received, March 28th*, 1950.]

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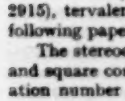
422. *Studies in Co-ordination Chemistry. Part V. Complexes of Bivalent and Tervalent Nickel with a Di(tertiary Arsine).*

By R. S. NYHOLM.

By using the di(tertiary arsine) chelate group, *o*-phenylenebisdimethylarsine, a series of bivalent nickel salts of the general formula $[Ni(Diarsine)_2]X_2$ has been prepared, where X = Cl, Br, I, CNS, or ClO_4. These salts, which vary in colour from red to brown, are diamagnetic and it is concluded that the four nickel–arsenic bonds are covalent and planar. Aerial oxidation of the bivalent chloride in the presence of hydrochloric acid yields a paramagnetic, complex salt containing tervalent nickel. The formula, $[NiCl_2(Diarsine)_2]Cl$, has been confirmed by the preparation of a perchlorate and a platinichloride and by conductimetric, potentiometric, and magnetic measurements. The last of these indicate the presence of one unpaired electron. The corresponding bromide and thiocyanate complexes of tervalent nickel have been prepared and are shown to have properties similar to those of the chloride. The corresponding paramagnetic iodide was not obtained but an unusual diamagnetic iodide complex is described. The properties of this new series of tervalent nickel salts are discussed and consideration is given to the bond orbitals used. An octahedral trisdiarsine complex of bivalent nickel of the formula $[Ni(Diarsine)_3][ClO_4]_2$ is described.

LITTLE previous work has been reported on the complexes of nickel with tertiary arsines and this investigation was undertaken to obtain information on the stereochemistry and stability of nickel complexes of the di(tertiary arsine) chelate group, *o*-phenylenebisdimethylarsine (I), with which both bivalent and tervalent iron have been shown to form stable complexes containing covalent bonds (Part III, *J.*, 1950, 851). This chelate group also forms strong covalent bonds with bivalent palladium (Chatt and Mann, *J.*, 1939, 1622), quadrivalent tin (Allison and Mann, *J.*, 1949, 2915), tervalent rhodium (Part IV, *J.*, 1950, 857) and bivalent and tervalent cobalt (Part VI, following paper).



(I.)

The stereochemistry of bivalent nickel is of special interest because octahedral, tetrahedral, and square complexes are known, but the element shows a distinct preference for the co-ordination number four, rather than six, particularly in its covalent compounds (Nyholm, *Quart.*

Reviews, 1949, **3**, 321). The factors which determine whether the configuration of a four-covalent complex will be tetrahedral or planar are imperfectly understood, but the importance of the electronegativity of the attached groups has been established. It was shown by Mellor and Craig (*J. Proc. Roy. Soc. N.S.W.*, 1941, **74**, 475; see also Mellor, *Chem. Reviews*, 1943, **33**, 137) that the tendency to form tetrahedral complexes increases as the electronegativity of the attached atoms increases. Using the magnetic criterion of bond type, these workers found that when four oxygen atoms were attached to the nickel atom the complexes were always tetrahedral but the presence of the less electronegative nitrogen or sulphur atom tended to give a square arrangement; they considered, however, that steric factors were also important. Table I shows how the magnetic moment may be used to distinguish between the square arrangement (using dsp^2 bonds) and the tetrahedral configuration. Magnetic data do not give the type of bond in a tetrahedral complex since both ionic and tetrahedral sp^3 covalent bonds lead to the presence of two unpaired electrons.

The powerful chelate group used here co-ordinates much more strongly with bivalent nickel than do trialkylarsines. Jensen (*Z. anorg. Chem.*, 1936, **229**, 265) has shown that triethylarsine does not form very stable compounds with bivalent nickel. He isolated the compound di-iodobistriethylarsinenickel(II), $NiI_2,2AsEt_3$, but this substance decomposed readily in benzene solution; the corresponding chloride and bromide dissociated in alcohol too extensively to permit of their isolation. By using the similar trialkylphosphines, Jensen (*loc. cit.*) obtained more stable compounds which had the general formula $NiX_2,2PR_3$, where R = alkyl and X = Cl, Br, I or NO_3. With the exception of the nitrate, which was green and had a dipole moment of 8·85 D., all of these compounds were red to brown and in benzene solution their dipole moments were zero. Jensen concluded that all of these compounds had a *trans*-planar configuration, except the nitrate which he considered was either *cis*-planar or tetrahedral. Asmussen ("Magnetokemiske Undersøgelser over Uorganiske Kompleksforbindelser," Copenhagen, 1944, p. 221) has reported that the magnetic moment of this compound is 3·05 B.M. which indicates the tetrahedral configuration (iii in Table I).

In their investigation of the complexes of bivalent palladium with this chelate group, Chatt and Mann (*loc. cit.*) isolated the salt-like complexes $[Pd(Diarsine)_2][PdCl_4]$ and $[Pd(Diarsine)_2]Cl_2$, and the non-ionic complex $[PdCl_2(Diarsine)]$ (cf. II). Attempts to prepare the nickel analogue (II) of this non-ionic complex have been unsuccessful. The stereochemistry of compounds of this type with different halogens would be of great interest.

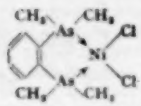
TABLE I.

Calculated magnetic moments for nickel complexes.

Complex.	Electronic arrangement. 3*d*	4*s*	4*p*		Calculated magnetic moment μ (B.M.).
(i) Nickelous covalent planar (dsp^2 bonds)	↑↓ ↑↓ ↑↓ ↑↓ ↑	↑↓	↑↓ ↑ ↑		0·0
(ii) Nickelous ionic, octahedral or tetrahedral	↑↓ ↑↓ ↑ ↑ ↑	↑↓	↑ ↑ ↑		2·83
(iii) Nickelous covalent tetrahedral (sp^3 bonds)	↑↓ ↑↓ ↑ ↑ ↑	↑↓	↑↓ ↑ ↑		2·83
(iv) Nickelous covalent octahedral (d^2sp^3 bonds)	↑↓ ↑↓ ↑ ↑ ↑	↑↓	↑↓ ↑↓ ↑↓	4*d*(?) ↓ ↓	2·83
(v) Nickelic covalent planar (dsp^2 bonds)	↑↓ ↑↓ ↑↓ ↑ ↑	↑↓	↑↓ ↑↓		1·73
(vi) Nickelic covalent octahedral (d^2sp^3 bonds)	↑↓ ↑↓ ↑ ↑ ↑	↑↓	↑↓ ↑↓ ↑↓	4*d*(?) ↓	1·73
(vii) Nickelic covalent square pyramid (dsp^3 bonds)	↑↓ ↑↓ ↑ ↑ ↑	↑↓	↑↓ ↑↓ ↑		1·73

When a solution of nickel chloride in alcohol was treated with the diarsine a deep blood-red colour developed instantly and the compound isolated had the formula $[Ni(Diarsine)_2]Cl_2$. This substance, which is diamagnetic, is soluble in water to give a red solution, which is partly hydrolysed as shown by the development of the odour of the diarsine. Addition of perchloric acid to the aqueous solution gives the insoluble perchlorate. The compound is formulated as (III), being di-(*o*-phenylenebisdimethylarsine)nickel(II) chloride. The corresponding bromide,

iodide, and thiocyanate were prepared and all these salts are diamagnetic. Their properties are summarised in Table II. The diamagnetism indicates the use of dsp^2 bonds from the nickel atom and hence it is concluded that the four nickel–arsenic bonds are coplanar.

(II.) 

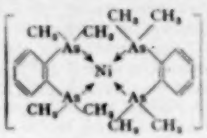
 (III.)

TABLE II.

Physical properties of bivalent and tervalent nickel complexes.

[A = *o*-Phenylenebis(dimethylarsine).]

Compounds of bivalent nickel.			Compounds of tervalent nickel.		
Complex.	Colour.	μ (B.M.).	Complex.	Colour.	μ (B.M.).
$[NiA_2]Cl_2$	Red	0·0	$[NiCl_2A_2]Cl$	Yellow	1·89
$[NiA_2]Br_2$	Brown	0·0	$[NiBr_2A_2]Br$	Orange	1·96
$[NiA_2](CNS)_2$	Reddish-brown	0·0	$[Ni(CNS)_2A_2]CNS$	Orange-brown	1·95
$[NiA_2](ClO_4)_2$	Buff-pink	0·0	$[NiCl_2A_2]ClO_4$	Yellow	1·94
$[NiA_2]I_2$	Dark brown	0·0			
			NiI_2A_2	Black	0·0

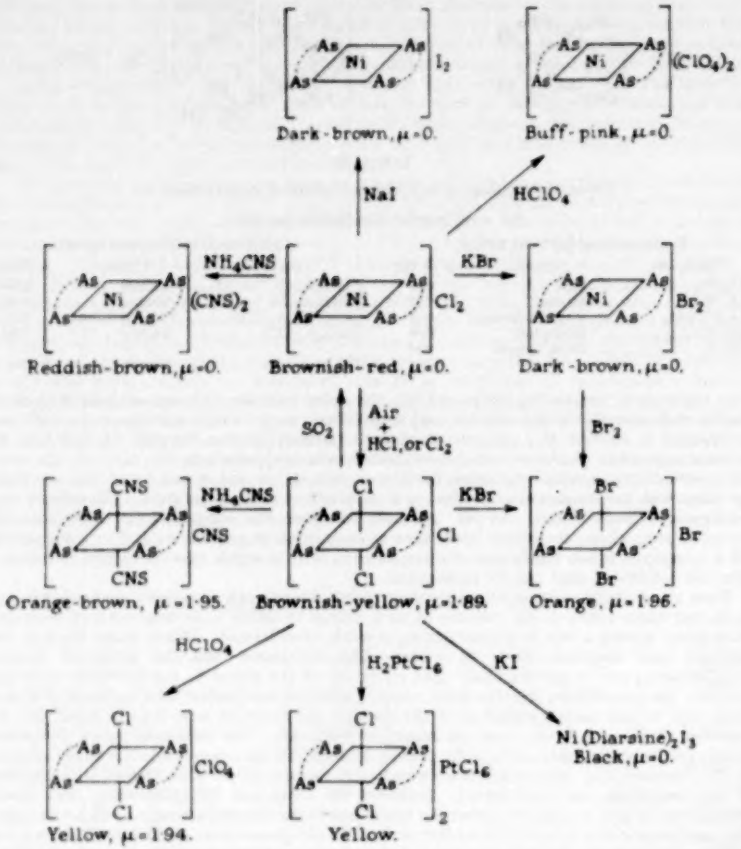
In attempts to prepare the compound (II), the nickel complex (III) was refluxed in alcoholic solution with excess of nickel chloride and hydrochloric acid. Chatt and Mann (*loc. cit.*) used this method to convert di-(*o*-phenylenebisdimethylarsine)palladous chloride (cf. III) into the non-ionic compound dichloro-(*o*-phenylenebisdimethylarsine)palladium (cf. II). In our work with nickel no precautions were taken initially to exclude air and it was found that oxidation took place with the formation of the first of a series of tervalent nickel salts. These have been investigated in some detail. As yet, attempts to obtain the compound (II) have been unsuccessful, even when precautions were taken to exclude air to prevent oxidation. Apparently such a compound is less stable than the bis(diarsine) salt, in which case the failure to isolate it under the conditions used can be understood.

When an alcoholic solution of the bivalent nickel chloride salt containing hydrochloric acid was heated under reflux in the presence of air a change in colour from deep red to a brownish-red occurred during a few hours and brown crystals were formed. When finely divided, this substance was brownish-yellow in colour. The compound had the empirical formula $NiCl_2(Diarsine)_2$ and it seemed likely that oxidation of the nickel to the tervalent state had occurred; the possibilities that the extra atom of chlorine was present as a molecule of hydrochloric acid or that partial oxidation of the diarsine had occurred were kept in mind, but the properties of the compound were incompatible therewith. The yellowish-brown compound was also produced in a less pure form by passing chlorine into an aqueous solution of the bivalent salt $[Ni(Diarsine)_2]Cl_2$; the red solution immediately became yellow when treated with chlorine, and the compound was precipitated. However, the compound $NiCl_2(Diarsine)_2$ itself reacts with chlorine to give a product containing more than three chlorine atoms, as will be discussed later, and hence this was not a convenient method for the preparation of the tervalent complex.

The compound dissolved readily in alcohol and was moderately soluble in water to give a green solution from which it was immediately reprecipitated by hydrochloric acid. This was taken to indicate that part, at least, of the chlorine was ionised. The aqueous solution was at first neutral to litmus. When kept for many hours the aqueous solution became orange and the odour of the diarsine developed; this hydrolysis was prevented by the addition of hydrochloric acid. The initial neutrality seemed to exclude the presence of hydrochloric acid in the molecule and it was observed that the diarsine does not react with hydrochloric acid by itself. The molecular conductivity of the aqueous solution at a dilution of 1024 litres was initially 120 mho; this figure gradually increased owing to hydrolysis but indicated the formation initially of two ions from each molecule of $NiCl_2(Diarsine)_2$. It thus seemed probable that the compound should be formulated as $[NiCl_2(Diarsine)_2]Cl$, (see Fig. 1), in which the tervalent nickel atom is octahedral. This formulation as dichlorodi-(*o*-phenylenebisdimethylarsine)-nickel(III) monochloride has been confirmed by other physical and chemical investigations to

be described. In Fig. 1 the two chlorine atoms in the cation are shown as *trans*; this is probably correct, but without an *X*-ray crystallographic examination it must remain speculative.

FIG. 1.



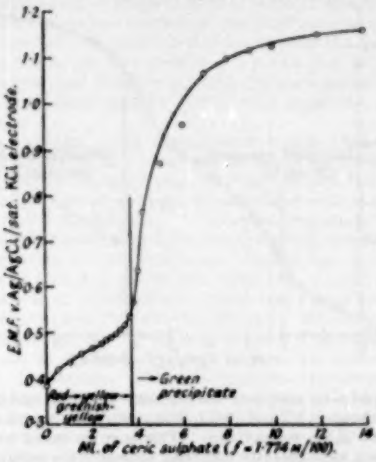
Treatment of the green solution of the complex in water with sulphur dioxide gave a red colour which suggested reduction to the bivalent nickel salt $[Ni(Diarsine)_3]Cl_2$. This was confirmed by the isolation of the buff-pink perchlorate of the bivalent complex, $[Ni(Diarsine)_3][ClO_4]_2$, which was identified by analysis and magnetic moment. This compound was also prepared by starting from a pure specimen of the bivalent nickel chloride complex and the two compounds are identical. When a solution of the tervalent complex was treated with perchloric acid a yellow precipitate of dichlorodi-(*o*-phenylenebisdimethylarsine)nickel(III) perchlorate, $[NiCl_2(Diarsine)_2]ClO_4$, was obtained. This compound is quite distinct from the perchlorate of the bivalent complex; whereas the compound $[Ni(Diarsine)_3][ClO_4]_3$ gave no precipitate on being heated with silver nitrate and nitric acid, the perchlorate of the tervalent complex soon lost the chlorine from the cation as silver chloride when similarly treated. Under these conditions the perchlorate ion does not react with silver nitrate. The platinichloride of

the tervalent nickel complex was also prepared and has the formula $[NiCl_2(Diarsine)_2]_2[PtCl_4]$ as required.

Potentiometric titration of the bivalent complex with ceric sulphate gives conclusive evidence that the oxidation involves a one-electron change per nickel atom. Fig. 2 shows the curve obtained by titrating a solution of di-(*o*-phenylenebisdimethylarsine)nickel(II) chloride with ceric sulphate at 0°, in the presence of a little hydrochloric acid. The chloride-ion concentration was kept low to prevent precipitation of the tervalent complex by the common-ion effect. Also, the titration was carried out at 0° to minimise hydrolysis since this produced the diarsine which is a reducing agent. Permanganate and dichromate gave high results, probably owing to greater simultaneous oxidation of the diarsine. From the curve it can be seen that there is a sudden increase in the oxidation potential at the calculated end-point. It

FIG. 2.

Potentiometric titration of $[Ni(Diarsine)_2]Cl_2$ *with ceric sulphate*; Pt *electrode.*



is possible to determine approximately the standard oxidation–reduction potential for the reaction

$$[Ni(Diarsine)_2]^{++} + 2Cl^- - e \longrightarrow [NiCl_2(Diarsine)_2]^+$$

from the figures obtained in this titration. The oxidation potential is given by the expression,

$$E = E_0 + \frac{RT}{F} \ln \frac{a_{[NiCl_2(Diarsine)_2]^+}}{a_{[Ni(Diarsine)_2]^{++}} \times a^2_{Cl^-}}$$

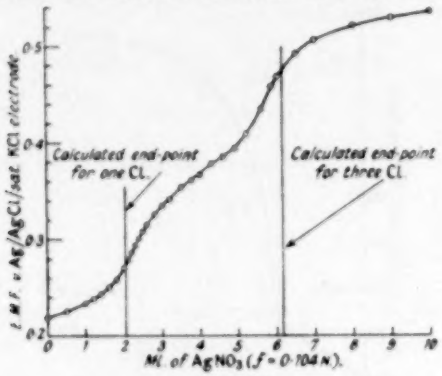
and hence the standard-oxidation reduction potential (E_0) is observed when all activities are unity. The activities of the oxidant and reductant are approximately equal when the bivalent nickel salt is 50% oxidised, but, as the activity of the chloride ion still affects the potential, it is possible to give E_0 to the nearest 0·1 v. only. By use of the above equation, E_0 is estimated to be *ca.* +0·7 v. on the standard hydrogen scale. This value explains why atmospheric oxygen can effect this oxidation: the reaction is thermodynamically feasible, since E_0 for the system $4e + O_2 + 4H^+ \longrightarrow 2H_2O$ is +1·23 v. The relative ease with which it occurs is unusual; the aerial oxidation of ferrous chloride in cold aqueous solution, for example, takes place only very slowly although E_0 for the system Fe^{++}/Fe^{+++} is +0·77 v. The conditions used in the present work are, however, much more favourable for oxidation; the solution is boiling and the substance formed by oxidation is less soluble. The alcohol also has an effect on the equilibrium and in any case the kinetics of the process may be quite different from those involved in the oxidation of ferrous chloride. The red solution became greenish-yellow at the end-point and further addition of ceric sulphate produced a green precipitate. A similar green compound is obtained

by the action of chlorine on an aqueous solution of the tervalent nickel complex salt and is possibly a derivative of quadrivalent nickel. This subject will be considered further in a later communication.

The result of a potentiometric titration using silver nitrate as titrant and a silver electrode as indicator is shown in Fig. 3. It was apparent from earlier experiments that the two chlorine atoms in the cation were not as strongly bound as in the similar tervalent rhodium salts (Part IV, *J.*, 1950, 857) or in the tervalent cobalt complex (Part VI, following paper), but by carrying out the titration in the presence of a large amount of alcohol it was possible to demonstrate that one of the three chlorine atoms reacted more readily than the other two. In Fig. 3 there is a definite inflexion in the curve after one equivalent of silver nitrate has been added, but on further addition of silver nitrate the other two chlorine atoms slowly react also.

FIG. 3.

Potentiometric titration of $[NiCl_2(Diarsine)_2]Cl$ *with* $AgNO_3$; *silver electrode.*


E.M.F. v. Ag/AgCl/sat. KCl electrode
0·5
0·4
0·3
0·2
Calculated end-point for one Cl.
Calculated end-point for three Cl.
0 1 2 3 4 5 6 7 8 9 10
Ml. of AgNO3 (f = 0·104 N).

The magnetic susceptibility supports the valency of three assigned to the nickel atom. The compounds $[NiCl_2(Diarsine)_2]Cl$ and $[NiCl_2(Diarsine)_2]ClO_4$ are paramagnetic with magnetic moments of 1·89 and 1·94 B.M., respectively. This may be taken to indicate the presence of one unpaired electron since experimental magnetic moments are usually a little in excess of the calculated value of 1·73 B.M. Oxidation of nickel to the tervalent state necessarily leaves it with an odd number of electrons and since a moment corresponding to one unpaired electron was observed it seems that only one of the electron pairs in the 3*d* shell has been uncoupled (see Table I). It must be pointed out that the magnetic moment does not indicate definitely which orbitals are used by the metal atom, but it does support a valency of three for the nickel. The orbitals used by the metal atom will be considered later.

Two other tervalent nickel complexes have been prepared from the chloride $[NiCl_2(Diarsine)_2]Cl$. When an aqueous solution of this compound was treated with sodium bromide, the orange complex salt dibromodi-(*o*-phenylenebisdimethylarsine)nickel(III) bromide was precipitated. This compound was also obtained, but less pure, by oxidising the bivalent bromide complex with bromine in alcohol. The compound was less soluble than the chloride in both water and alcohol; a suspension of it in aqueous alcohol was reduced by sulphur dioxide to the brown bivalent complex. The magnetic moment (1·96 B.M.) again showed the presence of one unpaired electron. The tervalent nickel thiocyanate was prepared similarly by the action of ammonium thiocyanate on an aqueous solution of the chloride and the compound dithiocyanatodi-(*o*-phenylenebisdimethylarsine)nickel(III) thiocyanate was precipitated as an orange-brown powder. The magnetic moment of this compound (1·95 B.M.) was similar to that of the chloride and bromide. This thiocyanato-complex began to decompose in a few days, but the tervalent nickel chloride and bromide were stable indefinitely. As shown in Table II, the tervalent nickel complexes were all paler than the corresponding bivalent planar compounds.

The reaction of the tervalent nickel chloride complex with sodium iodide takes quite a

different course from that of the bromide or thiocyanate, and a black compound of the empirical formula $NiI_2(Diarsine)_2$ was obtained. The very deep colour of this compound, compared with that of the bivalent iodide complex, suggested a different type of reaction and this was confirmed by the magnetic moment. Unlike the chloride, bromide, and thiocyanate of similar empirical formula, the compound was diamagnetic and it seemed possible that reduction to the bivalent state had occurred; such a reaction is to be expected from the oxidation–reduction potentials of the reactants. Since the oxidation potential of the couple $[NiCl_2(Diarsine)_2]^+/[Ni(Diarsine)_2]^{++}$ (*ca.* +0·7 v.) is higher than that of the couple I_2–I^- (+0·53 v.), oxidation of the iodide ion to iodine is expected with reduction of the nickel to the planar bivalent state, unless solubilities affect the equilibrium. Unless suitably stabilised, the iodides of metals in higher valency states are unstable; for example it was shown in Part III (*J.*, 1950, 851) that the iodide $[FeI_2(Diarsine)_2]I$, which is formed momentarily by the action of iodide ions on the ferric chloride complex, undergoes spontaneous oxidation–reduction to give the non-ionic octahedral ferrous complex $[FeI_2(Diarsine)_2]$. For this nickel complex, however, the reaction is not as simple, for no iodine is left in solution and its mode of attachment to the complex is doubtful. The diamagnetism seems to exclude the idea that the iodine is used to oxidise part of the diarsine, for it appears that the essential dsp^2 bonds from the four arsenic atoms to the metal are unaffected. The iodine could be present as I_3^- ions, but there is also the possibility that the compound is a polynuclear complex in which the polymerisation causes the diamagnetism. The deep colour lends some support to the latter suggestion, but these formulations remain at present speculative.

The stability of these tervalent nickel complexes is noteworthy. No value is available for the free energy of formation of a Ni^{+++} ion, but by comparison with cobalt, the oxidation potential of the couple Ni^{+++}–Ni^{++} must be near +2·0 v. At least it is known that the higher oxide of formula NiO_2 or Ni_2O_3 liberates oxygen when treated with acid, and this indicates an oxidation potential near +2·0 v. (Latimer, "Oxidation Potentials," Prentice Hall, N.Y., 1938, p. 190).* As the oxidation potential of the complex is only *ca.* +0·7 v., this decrease from +2·0 v. is a striking indication of the preferential stabilisation of the tervalent state. A qualitative demonstration of this is given by the behaviour of both complexes with water; the bivalent complex dissolves to a red solution which has a very pronounced odour of the di(tertiary arsine), which is produced by partial hydrolysis. Whereas, on the other hand, the green solution of the tervalent complex has initially no trace of an odour of the diarsine; after some hours the diarsine can be detected, but only because the hydroxy-complex formed by hydrolysis of the chloride decomposes. This decomposition is prevented by the addition of hydrochloric acid. Treatment of an aqueous solution of the bivalent complex with alcoholic dimethylglyoxime gave no precipitate until dilute aqueous ammonia was added to the solution, whereupon the usual red precipitate of bisdimethylglyoximenickel(II) was obtained. The tervalent complex, when similarly treated, gave no red precipitate initially but the solution developed a dark purple-red colour which may be due to a tervalent nickel complex with dimethylglyoxime. Jensen (private communication) has obtained such a complex by bromine oxidation of the bivalent complex. These experiments show that an aqueous solution of the compound $[NiCl_2(Diarsine)_2]Cl$ contains no bivalent nickel ion.

These nickel salts are the first examples of stabilised tervalent nickel complexes in which the metal atom is apparently octahedral. Jensen (*Acta Chem. Scand.*, 1949, **3**, 474) has recently investigated a relatively unstable non-ionic five-covalent complex of tervalent nickel which is formed when dibromo-*trans*-bistriethylphosphinenickel is oxidised with bromine. The compound has the formula $NiBr_2.2PEt_3$ and is monomeric in freezing benzene. The dipole moment in benzene is 2·3 D., which, together with the magnetic moment of 1·7—1·9 B.M., enabled Jensen to conclude that the complex has a square pyramidal structure. Daudel and Bucher (*J. Chim. physique*, 1945, **42**, 6) predicted that this shape would arise from the use of dsp^2 bonds by the metal atom, provided that the *d* orbital had a lower principal quantum number than the *s* and the *p* orbitals (see vii, Table I). Unlike the compounds described here, Jensen's complex decomposed within a few hours and thus an *X*-ray examination of its structure was not possible.

The compound tris-(*o*-phenylenebisdimethylarsine)nickel(II) perchlorate was obtained in small yield from the mother-liquors of the preparation of the tervalent chloride complex. The solution was still brownish-red after aerial oxidation for several weeks, and the addition of

* By using the value +0·59 v. for the Ni/Ni^{+++} couple (estimated by Pauling, "V. Henri Memorial Volume," Liege, 1948, p. 7) and the value −0·25 v. for the Ni/Ni^{++} (Latimer, *loc. cit.*) we obtain +1·77 v. for the Ni^{++}/Ni^{+++} couple.

perchloric acid gave the required compound as a red precipitate. Its properties are unusual in some ways: unlike the corresponding tris-*o*-phenanthroline– and trisdipyridyl–nickel complexes, for which $\mu = 2{\cdot}8$ B.M. (Asmussen, *op. cit.*, p. 212), this substance is diamagnetic. Also, chlorine and ceric sulphate, but not air, oxidise this substance to an unstable green compound. The properties of this bivalent nickel complex and its oxidation product are being investigated further.

The orbitals used in these nickelous and nickelic complexes are of considerable interest. The diamagnetic four-covalent complexes obviously use dsp^2 bonds and are hence square, but the tervalent complexes are not so straightforward as it is not easy to decide which orbital is occupied by the unpaired electron. This unpaired electron could be in the 3*d* shell, in which case the use of d^2sp^3 bonding orbitals is not permissible (see vii, Table I), or it could be promoted to some level above 4*p*, thereby enabling the metal atom to use the d^2sp^3 bond orbitals (vi, Table I).

With regard to the former possibility, it is conceivable that the first step in the oxidation of the square complex is the unpairing of the fourth 3*d* electron pair, it being assumed that the four $3d4s4p^2$ bonds are unaffected. The unpaired electron so obtained would then form a bond in the remaining 4*p* orbital, giving five dsp^2 bonds (see vii, Table I); then would follow immediately the accession to the cation of another chloride ion, to be held by an essentially ionic bond, giving a co-ordination number of six. Actually, the two chlorine atoms would probably be *trans* and some form of resonance between the two chlorine atoms would occur. This attainment of a co-ordination number of six is in keeping with the tendency of metals to reach the four- or six-covalent state when possible; this was not possible with Jensen's compound $NiBr_2.2PEt_3$ because the oxidation was carried out under anhydrous conditions where no anions were available to enter the co-ordination sphere. This method of formulation would explain the ease with which the two chlorine atoms in the cation reacted with silver nitrate.

The other possibility is that d^2sp^3 covalent bond orbitals are used with the promotion of the unpaired electron to the 4*d* shell (probably), as shown in vi, Table I. Some support is provided for this idea by preliminary experiments which suggest that this electron may be removed by oxidation, to give a quadrivalent nickel complex as would be expected. It must be emphasised however, that it is not yet possible to decide between these two hypotheses.

Fig. 1 summarises the relations between these nickel complexes; in each case the formula for the di(tertiary arsine) has been abbreviated to show only the two arsenic atoms.

Experimental.

Di-(o-phenylenebisdimethylarsine)nickel(II) *Chloride.*—Nickel chloride hexahydrate (1·5 g.) was dissolved in hot alcohol (30 ml.) and treated with *o*-phenylenebisdimethylarsine (2·0 g.) in alcohol (20 ml.). The blood-red solution which formed was heated on the water-bath for a few seconds and most of the alcohol then distilled off under reduced pressure at room temperature until the volume was about 10 ml. Brownish-red crystals had begun to separate, and, after cooling in ice water, the mixture was filtered and the *complex* (1·5 g.) washed many times with small quantities of alcohol, in which it was fairly soluble. The substance was then dried in a vacuum-desiccator and kept dry (Found: C, 34·2; H, 4·9; Cl, 10·2. $C_{20}H_{32}Cl_2As_4Ni$ requires C, 34·3; H, 4·6; Cl, 10·1%). Magnetic susceptibility: powder form, at 28°, $\chi = -0{\cdot}50 \times 10^{-6}$, whence $\mu = 0$. The complex dissolved readily in water to give a red solution which had a strong odour of the diarsine. It was insoluble in non-hydroxylic solvents such as benzene. An aqueous or alcoholic solution reacted instantly with silver nitrate, all of the chloride ion being precipitated.

Di-(o-phenylenebisdimethylarsine)nickel(II) *Bromide.*—Nickel chloride hexahydrate (1·3 g.) and sodium bromide (2·5 g.) were dissolved, by heating, in alcohol (40 ml.) containing distilled water (20 ml.) and the solution was filtered and treated with *o*-phenylenebisdimethylarsine (2·8 g.) in alcohol (30 ml.). The solution immediately developed a dark red colour and, after the solution had been warmed and shaken for a few seconds, beautiful, sparkling, brown plates crystallised. The solution was heated on the water-bath for a few minutes and then filtered, and the compound was well washed with alcohol in which it was slightly soluble to give a pink solution. The *complex* (3·4 g.) was finally dried in a vacuum-desiccator (Found: C, 31·1; H, 4·1; Br, 20·0. $C_{20}H_{32}Br_2As_4Ni$ requires C, 30·3; H, 4·0; Br, 20·2%). Magnetic susceptibility: powder form, at 20°, $\chi = -0{\cdot}46 \times 10^{-6}$, whence $\mu = 0$. The compound was much less soluble than the chloride in both water and alcohol, and was insoluble in solvents such as benzene. Treatment of an alcoholic solution with silver nitrate caused precipitation of all the bromide ion.

Di-(o-phenylenebisdimethylarsine)nickel(II) *Thiocyanate.*—Nickel chloride hexahydrate (0·22 g.) was dissolved in hot alcohol (30 ml.), and ammonium thiocyanate (2·0 g.) in distilled water (5 ml.) added. The hot solution was filtered and added to *o*-phenylenebisdimethylarsine (0·6 g.) in alcohol (20 ml.). The brownish-violet solution immediately became red, and dark brown crystals were precipitated. These were filtered off (0·55 g.) and well washed with alcohol, in which the *thiocyanate* dissolved slightly to give a pinkish-violet solution (Found: C, 35·6; H, 4·35; N, 3·9; S, 8·4; Ni, 8·1. $C_{22}H_{32}N_2S_2As_4Ni$ requires C, 35·4; H, 4·3; N, 3·8; S, 8·6; Ni, 7·9%). The compound was insoluble in water, but an alcoholic solution reacted immediately with silver nitrate to give a white precipitate.

In the above preparation a slight excess of the diarsine was used. If the nickel halide is in excess, an impure product is obtained, the analysis of which suggests that the impurity is almost certainly the tetrathiocyanatonickel(II) compound $[Ni(diarsine)_3][Ni(CNS)_4]$. As a further precaution to avoid the formation of this substance, the nickel solution was always added to the excess of diarsine.

Magnetic susceptibility: powder form; as there was insufficient of the compound to fill the tube, the susceptibility was not measured exactly but the compound was diamagnetic, whence $\mu = 0$.

Di-(o-phenylenebisdimethylarsine)nickel(II) *Iodide*.—Nickel chloride hexahydrate (1·2 g.) and lithium iodide (4 g.) were dissolved in alcohol (50 ml.), and the hot solution filtered and treated with *o*-phenylenebisdimethylarsine (1·4 g.) in alcohol (60 ml.). A blood-red colour developed immediately and, after warming and stirring of the solution, a brown precipitate formed. The solution was heated on the water-bath for a few minutes and, after standing for a short time, the precipitate was filtered off and washed many times with alcohol in which it was only very slightly soluble. The *iodide* (2·2 g.) was then dried in a vacuum-desiccator (Found: C, 27·3; H, 3·8; I, 28·8. $C_{20}H_{32}I_2As_4Ni$ requires C, 27·1; H, 3·6; I, 28·7%). Magnetic susceptibility: powder form: the compound was diamagnetic, but the susceptibility was not measured exactly, whence $\mu = 0$. The compound was only slightly soluble in water.

Di-(o-phenylenebisdimethylarsine)nickel(II) *Perchlorate*.—The bivalent nickel chloride complex (prepared as above) (0·2 g.) was dissolved in distilled water (10 ml.), to give a red solution, an excess of 30% perchloric acid was added immediately and the solution then diluted with distilled water (40 ml.). A buff-pink precipitate formed at once, and the odour of the diarsine, which is characteristic of a solution of the chloride complex disappeared. The precipitated *perchlorate* was filtered off, washed many times with distilled water, in which it was insoluble, and dried in a vacuum-desiccator. A practically quantitative yield of just over 0·2 g. was obtained (Found: C, 29·3; H, 4·0; Ni, 7·2. $C_{20}H_{32}O_8Cl_2As_4Ni$ requires C, 29·0; H, 3·9; Ni, 7·1%).

Dichlorodi-(o-phenylenebisdimethylarsine)nickel(III) *Chloride*.—Nickel chloride hexahydrate (1·6 g.) was dissolved in alcohol (60 ml.) containing 10N-hydrochloric acid (7 ml.), and a solution of *o*-phenylenebisdimethylarsine (2·9 g.) in alcohol (30 ml.) was added. The blood-red solution was then refluxed, filtered air being allowed access to the surface of the solution. After about 2 hours brown crystals formed on the surface of the flask, but refluxing was continued for about 2 days. The solution was then cooled and filtered, and the compound washed many times with dilute hydrochloric acid and finally with alcohol. The washings were at first red and finally yellowish-green owing to a little of the *complex* dissolving. The substance (2·4 g.) was then dried in a vacuum-desiccator (Found: C, 32·5; H, 4·5; Cl, 14·4; Ni, 8·05. $C_{20}H_{32}Cl_2As_4Ni$ requires C, 32·6; H, 4·3; Cl, 14·5; Ni, 8·0%). An aqueous solution of the complex was green, but when kept it became orange after a few days, and during this time the odour of the diarsine developed in the solution. Addition of hydrochloric acid to an aqueous solution of the compound gave a yellow precipitate immediately, and this was a convenient method of purification. The substance is brown in the form of crystals, but when powdered has a yellowish-brown colour. It was quite insoluble in benzene or chloroform, but dissolved readily in alcohol.

The following results were obtained in determinations of the magnetic susceptibility of the powder form of four separately prepared specimens:

Temp.	$\chi \times 10^6$.	$\chi_M \times 10^6$.	$\chi_M \times 10^6$ (at 20°).	χ_M + Diamagnetic correction (452).	Magnetic moment, μ (B.M.).
21°	1·39	1024	1030	1482	1·87
27·5	1·51	1110	1140	1592	1·94
26·5	1·42	1040	1060	1512	1·89
20	1·41	1040	1040	1492	1·88
				Mean magnetic moment = 1·89 B.M.	

Dichlorodi-(o-phenylenebisdimethylarsine)nickel(III) *Platinichloride*.—A solution of the tervalent nickel monochloride complex $[NiCl_2(diarsine)_2]Cl$ (0·25 g.) in alcohol (50 ml.) was filtered, and an excess of a 10% aqueous solution of chloroplatinic acid added. A yellow precipitate of the *platinichloride* was formed immediately and, after coagulation by warming, this was filtered off and washed many times with distilled water and dried in a vacuum-desiccator (0·25 g.) (Found: C, 26·5; H, 3·7; Ni, 6·5; Pt, 10·6; Cl, 19·2. $C_{20}H_{32}Cl_{10}As_4Ni_2Pt$ requires C, 26·5; H, 3·5; Ni, 6·5; Pt, 10·66; Cl, 19·6%). Insufficient of the material was available for a determination of the magnetic moment.

Dichlorodi-(o-phenylenebisdimethylarsine)nickel(III) *Perchlorate*.—The tervalent nickel monochloride complex, $[NiCl_2(Diarsine)_2]Cl$ (0·7 g.), was moistened with alcohol and dissolved quickly in warm distilled water (200 ml.). The solution was filtered and the filtrate treated immediately with excess of a 30% solution of perchloric acid, with vigorous stirring. A yellow precipitate was obtained which settled after a few minutes. It was then filtered off and washed thoroughly with cold distilled water, in which it was practically insoluble. The *complex* (0·7 g.) was then dried in a vacuum desiccator and then had a brownish-yellow colour with a golden sheen (Found: C, 29·9; H, 3·8; Cl, 13·1; Ni, 7·5. $C_{20}H_{32}O_8Cl_2As_4Ni$ requires C, 29·95; H, 4·0; Cl, 13·3; Ni, 7·3%). Magnetic susceptibility: powder form, at 16°: $\chi = 1·48 \times 10^{-6}$, $\chi_M = 1180 \times 10^{-6}$, correction for diamagnetism = 459×10^{-6}, whence $\mu = 1·94$ B.M.

Dibromodi-(o-phenylenebisdimethylarsine)nickel(III) *Bromide*.—The tervalent nickel monochloride complex, $[NiCl_2(Diarsine)_2]Cl$ (1·1 g.), was dissolved in warm water (300 ml.) as quickly as possible, after being first moistened with alcohol, and the solution filtered. The filtrate was treated immediately with a solution of sodium bromide (3 g.) in distilled water (10 ml.), with constant stirring. An orange-yellow precipitate appeared at once and, after a few minutes' stirring, this coagulated to an orange-brown, crystalline powder. This *bromide* (1·3 g.) was filtered off, washed many times with distilled

water, in which it was only very slightly soluble, and dried in a vacuum-desiccator (Found: C, 27·6; H, 3·8; Br, 27·6; Ni, 6·9. $C_{39}H_{33}Br_2As_3Ni$ requires C, 27·6; H, 3·7; Br, 27·6; Ni, 6·75%). Magnetic susceptibility: powder form at 17°: $\chi = 1{\cdot}33 \times 10^{-6}$, $\chi_M = 1160 \times 10^{-6}$, correction for diamagnetism = 489×10^{-6}, whence $\mu = 1{\cdot}96$ B.M. The compound could be recrystallised from a large volume of alcohol containing a little hydrobromic acid. It was less soluble than the chloride in both water and alcohol, and was quite insoluble in benzene and chloroform.

Dithiocyanatodi-(o-phenylenebisdimethylarsine)nickel(III) *Thiocyanate.*—The tervalent nickel chloride complex, $[NiCl_2(Diarsine)_2]Cl$ (1·0 g.), was moistened with alcohol and dissolved quickly in warm distilled water (30 ml.). The solution was stirred vigorously and ammonium thiocyanate (3 g.) added; an orange-brown precipitate then formed at once. The solution was set aside for about 10 minutes with constant stirring, after which the *thiocyanate* had settled out. It (1·1 g.) was filtered off, well washed with cold distilled water, in which it was very slightly soluble, and dried in a vacuum-desiccator (Found: C, 34·3; H, 4·1; N, 4·6; S, 11·3; Ni, 7·3. $C_{39}H_{38}N_2S_2As_4Ni$ requires C, 34·3; H, 4·0; N, 5·2; S, 11·9; Ni, 7·3%). The compound dissolved in warm alcohol to an orange solution which reacted immediately with silver nitrate to give a white precipitate in a green solution. The solubility of this tervalent nickel complex in alcohol was greater than that of the bivalent complex. The compound had to be analysed and the magnetic moment determined as soon as it was prepared, for after a few days decomposition was apparent, the odour of organic sulphur compounds being detected. Magnetic susceptibility: powder form at 14°: $\chi = 1{\cdot}45 \times 10^{-6}$, $\chi_M = 1170 \times 10^{-6}$, correction for diamagnetism = 490×10^{-6}, whence $\mu = 1{\cdot}95$ B.M.

Di-(o-phenylenebisdimethylarsine)nickel Tri-iodide.—The tervalent nickel chloride complex, $[NiCl_2(Diarsine)_2]Cl$ (1·4 g.), was dissolved in distilled water (350 ml.) as quickly as possible by gentle warming, and the solution filtered and treated at once with sodium iodide (5 g.) in distilled water (20 ml.). The green solution first became brown and then a black precipitate was formed. The latter was allowed to coagulate for a few minutes, then filtered off, and washed many times with distilled water until the washings had only a faint pink colour. The *complex* (1·7 g.) was dried in a vacuum-desiccator (Found: C, 23·7; H, 3·4; I, 37·9; Ni, 5·9. $C_{39}H_{38}I_3As_4Ni$ requires C, 23·7; H, 3·2; I, 37·6; Ni, 5·8%). Although insoluble in cold water or alcohol, the substance was slightly soluble in hot aqueous alcohol to a pink solution. Magnetic susceptibility: powder form at 22°: $\chi = -0{\cdot}46 \times 10^{-6}$, whence $\mu = 0$.

Tris-(o-phenylenebisdimethylarsine)nickel(II) *Perchlorate.*—This compound was obtained in a slightly impure form from the mother-liquors of the preparation of the tervalent nickel chloride complex. The red residues from several preparations of the compound $[NiCl_2(Diarsine)_2]Cl$ were treated with filtered air for about 3 weeks, a little extra hydrochloric acid being added to the solution. After this time the solution was still reddish-brown and a little more of the tervalent complex had crystallised out. The solution was then filtered, diluted to about 70 ml. with distilled water, and treated with excess of 30% perchloric acid. A reddish precipitate was obtained which was filtered off and well washed with distilled water, in which it was only very slightly soluble to give a pink solution. The filtrate was initially green owing to the excess nickel chloride present. The *perchlorate* was then dried in a vacuum-desiccator, the colour changing from red to brown, possibly owing to the loss of water of crystallisation (Found: C, 32·3; H, 4·2; Cl, 7·0; Ni, 5·55. $C_{39}H_{44}O_4Cl_2As_6Ni$ requires C, 32·3; H, 4·3; Cl, 6·4; Ni, 5·25%). The compound was soluble in warm water to give a red solution, but was insoluble in other solvents. It gave only a slight precipitate (corresponding to about 0·2—0·3% of chlorine) with silver nitrate and nitric acid after prolonged heating, showing that a trace of $[NiCl_2(Diarsine)_2]ClO_4$ probably was present. The perchlorate ion does not react with silver nitrate under the above conditions. Magnetic susceptibility: powder form at 21·5°: $\chi = -0{\cdot}38 \times 10^{-6}$, whence $\mu = 0$.

Potentiometric Titrations.—Oxidation–reduction. The red bivalent complex $[Ni(Diarsine)_2]Cl_2$ (0·0451 g.) was dissolved in ice-cold distilled water (50 ml.), 10N-hydrochloric acid (0·2 ml.) added, and the solution stirred vigorously in a 250-ml. vessel immersed in ice-water. A bright platinum electrode was placed in the solution which was connected to a silver–silver chloride–saturated potassium chloride electrode through a potassium chloride agar bridge. Ceric sulphate (0·01774N.) was run in immediately, the minimum time elapsing between dissolution of the compound and the titration. The result of the titration is shown in Fig. 2.

Chloride ion. The tervalent nickel chloride complex (0·1565 g.), was dissolved in absolute alcohol (70 ml.) and distilled water (30 ml.), and N-nitric acid (10 ml.) added just before titration. The solution was stirred vigorously in a 250-ml. vessel. A silver–silver chloride electrode was inserted and the solution connected to a silver–silver chloride–saturated potassium chloride reference electrode through an ammonium nitrate agar bridge. The temperature throughout was 20°. The solution was then titrated with silver nitrate solution (0·104N.) from a microburette. The results are shown in Fig. 3. It was necessary to use a high concentration of alcohol in the solvent for this titration, otherwise after the addition of 1 equivalent of silver nitrate no inflexion was observed.

Molecular Conductivity of Tervalent Nickel Chloride Complex.—Measurements were carried out in a pipette-type cell of volume about 15 ml. and cell constant 0·0508 $cm.^{-1}$; the conductivity water used had a specific conductance of $1{\cdot}3 \times 10^{-6}$ $mho/cm.^3$ at 25°. The tervalent nickel chloride complex $[NiCl_2(Diarsine)_2]Cl$ (0·0720 g.) was well dried and finely powdered to hasten dissolution, and dissolved quickly in about 50 ml. of warm conductivity water and the solution adjusted to 100 ml. at 25°. This gave a solution containing one g.-mol. per 1024 l. The cell was then filled and the conductivity measured at 25° in a thermostat. Three lots of the solution were used, and the results showed that the conductivity increased a little more rapidly with time when the solution was in the cell than when kept in a flask in the thermostat; a slight catalytic effect of the platinum may be responsible, but in any case the differences were small and may not be significant. By extrapolation to zero time it is concluded that the initial molecular conductivity of the M/1024-solution was 120 mho, and hence it follows that the

complex forms two ions in solution. The solution gradually lost the green colour, becoming first yellow, then finally orange-red, and the odour of the diarsine was observed after this decomposition had occurred. The following figures show how the molecular conductivity increased with time :

Solution no.	Time (mins.).	Molecular conductivity, mho.	Solution no.	Time (mins.).	Molecular conductivity, mho.
1	0	120 (estim.)	3	183	149 (estim.)
1	42	124	3	218	157
1	47	127	3	233	159
1	78	135	3	271	164
2	83	136	3	358	175
2	85	139	3	1598	269
2	91	143	3	2173	373
3	95	137	3	3073	450
3	105	142	3	3388 (2½ days)	450

Reduction of the Tervalent Nickel Chloride Complex.—The monochloride $[NiCl_2(Diarsine)_2]Cl$ (0·3 g.) was dissolved in distilled water (125 ml.) and filtered at once. Sulphur dioxide was passed into the green solution. Within a minute the solution became orange; finally it was red. After five minutes (to ensure that reduction was complete), excess of a 60% solution of perchloric acid was added and a buff-pink precipitate of the bivalent perchlorate $[Ni(Diarsine)_2](ClO_4)_2$ was obtained. This was filtered off and well washed with distilled water and identified by analysis (Found : C, 29·3; H, 3·8; Ni, 7·1. Calc. for $C_{28}H_{32}O_8Cl_2As_4Ni$: C, 29·0; H, 3·9; Ni, 7·1%). The compound was diamagnetic as required for a planar four-covalent complex of bivalent nickel.

Analysis.—Halogen was determined by heating about 0·1—0·2 g. of the compound with 20 ml. of 0·05N-silver nitrate in the presence of about 10 ml. of 15N-nitric acid on the water-bath until decomposition was complete. The excess of silver nitrate was then determined with standard ammonium thiocyanate solution. Total halogen in perchlorates was determined by the Carius method.

Nickel was determined by dimethylglyoxime after oxidation of organic matter and removal of the arsenic. About 0·2 g. of the compound was folded in a small filter paper and digested in a Kjeldahl flask with potassium sulphate (5 g.) and concentrated sulphuric acid (10 ml.). When the solution had become clear, distilled water (150 ml.) was added and the arsenic precipitated with hydrogen sulphide. The arsenious sulphide was then filtered off and the excess of hydrogen sulphide removed by boiling. The nickel was then precipitated with dimethylglyoxime in the usual manner and weighed.

Microanalyses for carbon, hydrogen, nitrogen, and sulphur were carried out by Messrs. Weiler and Strauss, Oxford.

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423. *Studies in Co-ordination Chemistry. Part VI. Complexes of Bivalent and Tervalent Cobalt with a Di(tertiary Arsine).*

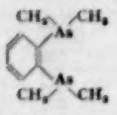
By R. S. NYHOLM.

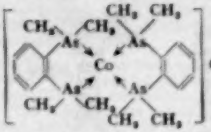
A series of complex salts of bivalent and tervalent cobalt with the di(tertiary arsine) chelate group, *o*-phenylenebisdimethylarsine, has been prepared and studied. Cobaltous halides form stable, slightly soluble salts of the formula $[Co(Diarsine)_2]X_2$, where X = Cl, Br, I, or CNS. From the magnetic moments of these compounds it is concluded that the four bonds to the cobalt atom are covalent and planar. Aerial oxidation of these cobaltous salts gives very stable tervalent octahedral complexes, in which the diamagnetic cation contains two halogen atoms and two molecules of the chelate group attached to a cobaltic atom; the anion may be either a halogen atom or the group $[CoX_4]^-$, where X = Cl or CNS. The chloride, bromide, iodide, and thiocyanate complexes have been prepared and their properties are discussed. The behaviour of iron, cobalt, and nickel with this di(tertiary arsine) are compared.

In previous papers (Parts III, IV, and V, *J.*, 1950, 851, 857, 2061) the complexes of iron, rhodium, and nickel with the chelate group *o*-phenylenebisdimethylarsine (I) were investigated, and their stereochemistry was determined. It was decided to investigate the complexes of bivalent and tervalent cobalt with this chelate group since compounds of tertiary arsines with cobalt had not been described previously. With the results of this investigation available it is possible to compare and contrast the compounds of iron, cobalt, and nickel with this di(tertiary arsine);

all of these elements from covalent bonds with this chelate group in both the tervalent and the bivalent state.

(I.)





(II.)

The stereochemistry of bivalent cobalt is of unusual interest since octahedral complexes (both covalent and ionic), planar four-covalent complexes, and tetrahedral complexes are known. When the compound is tetrahedral, the magnetic moment does not enable one to decide whether the bonding is ionic or covalent using sp^3 bonds, because the number of unpaired electrons is the same in both cases (see i and ii in Table I). The octahedral complexes usually have ionic bonds with magnetic moments between 4 and 5 B.M., *e.g.*, $[Co(NH_3)_6]Cl_2$ has a magnetic moment

TABLE I.

Calculated magnetic moments for cobalt complexes.

Complex.	Electronic arrangement. 3*d*	4*s*	4*p*	4*d*(?)	Calculated magnetic moment μ (B.M.).
(i) Cobaltous (ionic) (tetrahedral or octahedral)	↓↑ ↓↑ ↓↑ ↓ ↓	□	□ □ □		3·88
(ii) Cobaltous (tetrahedral) (sp^3 bonds)	↓↑ ↓↑ ↓↑ ↓ ↓	↓↑	↓↑ ↓↑ ↓↑		3·88
(iii) Cobaltous, planar (dsp^2 bonds)	↓↑ ↓↑ ↓↑ ↓↑ ↓	↓↑	↓↑ ↓↑ □		1·73
(iv) Cobaltous, octahedral (d^2sp^3 bonds)	↓↑ ↓↑ ↓↑ ↓↑ ↓↑	↓↑	↓↑ ↓↑ ↓↑	↓	1·73
(v) Cobaltic (ionic)	↓↑ ↓↑ ↓ ↓ ↓	□	□ □ □		4·90
(vi) Cobaltic, octahedral (d^2sp^3 bonds)	↓↑ ↓↑ ↓↑ ↓↑ ↓↑ ↓	↓↑	↓↑ ↓↑ ↓↑		0·0

of 5·25 B.M. (Klemm and Schuth, *Z. anorg. Chem.*, 1933, **210**, 33), but at least one octahedral complex with covalent bonds is known. This is the compound dipotassium calcium hexanitrocobalt(II) $[K_2CaCo(NO_2)_6]$ for which Cambi, Ferrari, and Colla (*Gazzetta*, 1936, **65**, 1162) reported a magnetic moment of 1·9 B.M. As may be seen from Table I (iv) the calculated magnetic moment for an octahedral complex of bivalent cobalt with covalent bonds is 1·73 B.M., corresponding to one unpaired electron. A magnetic moment of 1·73 is also predicted for planar four-covalent complexes because this shape requires the use of dsp^2 bonds (see iii, Table I).* It should thus be easy to distinguish between planar four-covalent complexes and tetrahedral complexes by magnetic susceptibility measurements, since the magnetic moments are so different (1·73 B.M., compared with 3·88 B.M.). In practice the magnetic moments of both the square and the tetrahedral complexes are rather larger than these figures, probably owing to a considerable orbital contribution to the magnetic moment (Selwood, "Magnetochemistry," Interscience N.Y., 1943, p. 163). Mellor and Craig (*J. Proc. Roy. Soc. N.S.W.*, 1940, **74**, 495) reported magnetic moments between 1·8 and 2·8 B.M. for a series of planar complexes, and values between 4·2 and 5·3 B.M. for tetrahedral complexes; Selwood (*ibid.*, p. 174) and Pauling ("Nature of the Chemical Bond," N.Y., 1945, p. 114) have reported similar values. When the bonds are ionic, bivalent cobalt forms either octahedral, *e.g.*, $[Co(NH_3)_6]Cl_2$, or tetrahedral complexes, *e.g.*, $M^I_2[CoCl_4]$. The co-ordination number is, as a rule, six in cationic complexes, and four in anionic complexes. When the cobalt atom forms covalent bonds the co-ordination number four is more common than six. Little is known of the conditions leading to square complexes; it seems, however, that if the co-ordination number is four then planar complexes are obtained only when the cobalt atom is joined to the less electro-negative atoms. Mellor and Craig (*loc. cit.*) found that four sulphur atoms tended to give the planar arrangement,

* Calvin and his co-workers (*J. Amer. Chem. Soc.*, 1946, **68**, 2254) have shown recently by use of *X*-rays that certain four-covalent complexes of bivalent cobalt with one unpaired electron are planar.

but four oxygen atoms gave the tetrahedral configuration. It is apparent that bivalent cobalt forms square complexes less readily than does bivalent nickel, and increasing the electronegativity of the attached groups results in a change to the tetrahedral configuration more readily in the former case; for example, although the compound $NiCl_2.2PEt_3$ is planar, $CoCl_2.2PEt_3$ is tetrahedral.

Although no complexes of bivalent cobalt with tertiary arsines have been reported previously, Jensen (*Z. anorg. Chem.*, 1936, **229**, 282) described the compound dichlorobistriethylphosphinecobalt(II), $CoCl_2.2PEt_3$, as well as the tripropylphosphine analogue, but he made no reference to the corresponding tertiary arsine complex. These phosphine complexes were unstable. Tertiary arsines usually form complexes similar to those given by tertiary phosphines, but as a rule the arsine complexes are less stable: with bivalent nickel, for example, the only tertiary arsine complex isolated by Jensen (*ibid.*, p. 265) had the formula $NiI_2.2AsEt_3$, but this was less stable than the corresponding phosphine compound. For the compound $CoCl_2.2PEt_3$, Jensen (*ibid.*, p. 282) reported a dipole moment of 8·7 D. in benzene solution; this was taken to indicate the tetrahedral configuration rather than the less likely *cis*-planar arrangement, and the magnetic moment of this compound, 3·5 B.M. (Jensen, private communication), seems to confirm this.

When a solution of cobaltous chloride in alcohol was treated with the di(tertiary arsine), one obtained immediately a yellow precipitate of the compound di-(*o*-phenylenebisdimethylarsine)-cobalt(II) chloride, $[Co(Diarsine)_2]Cl_2$, see (II). This substance was insoluble in benzene or chloroform, but was slightly soluble in warm water or warm alcohol. The aqueous solution reacted at once with silver nitrate, showing that the chlorine was ionised, but the low solubility in water, combined with the pronounced hydrolysis, vitiated attempts to determine the molecular conductivity. These properties support the assignment of the salt-like structure to this compound, and, as the magnetic moment (2·1 B.M.) indicated the presence of one unpaired electron, the four dsp^2 cobalt–arsenic bonds are apparently planar (see iii, Table I). The bromide, iodide, and thiocyanate were prepared in a similar manner, and had magnetic moments which indicated the presence of one unpaired electron (see figure). These compounds were only very slightly soluble in water and their colours varied from yellow to brown. The colour is some guide to the stereochemistry, for Mellor and Craig (*loc. cit.*) noticed that square complexes of bivalent cobalt were some shade of brown while the ionic or tetrahedral complexes varied in colour from pink or mauve to blue; the correlation between colour and magnetic susceptibility is, however, not so well established as with the corresponding compounds of nickel. The moist chloride became green on the surface in air, owing to oxidation, and all of these bivalent complexes oxidised readily in air to give very stable complexes of tervalent cobalt.

Attempts to isolate a non-ionic complex of the formula $[Co(Hal)_2.Diarsine]$ by refluxing an alcoholic solution of cobaltous chloride with the complex salt $[Co(Diarsine)_2]Cl_2$ in an inert atmosphere were unsuccessful. When air was admitted to the reaction mixture, oxidation took place rapidly and the cobaltous salt dissolved to give a green solution from which a green complex of tervalent cobalt was obtained on cooling. The formula of this substance, $Co_3Cl_8(Diarsine)_4$, indicates that two cobaltic and one cobaltous atom are present. The mean magnetic moment is 2·7 B.M., but on the assumption that the two cobaltic atoms are diamagnetic the moment of the cobaltous atom is 4·4 B.M. The low solubility of the compound suggested that it was a salt, and it was found that half the chlorine could be titrated with silver nitrate in alcohol solution. These facts suggested the formula $[CoCl_2(Diarsine)_2]_2[CoCl_4]$, namely bis[dichlorodi-(*o*-phenylenebisdimethylarsine)cobalt(III)] tetrachlorocobalt(II), and this was confirmed by chemical investigations. When a solution of the compound in alcohol was treated with perchloric acid the $[CoCl_4]^{=}$ ion was replaced and the blue-green diamagnetic compound dichlorodi-(*o*-phenylenebisdimethylarsine)cobalt(III) perchlorate, $[CoCl_2(Diarsine)_2]ClO_4$, was precipitated. By subtracting the diamagnetic susceptibility of the cation in this compound from the magnetic susceptibility of the compound $[CoCl_2(Diarsine)_2]_2[CoCl_4]$ one obtains the magnetic susceptibility of the $[CoCl_4]^{=}$ ion. These figures are given in Table II and the magnetic moment of the $[CoCl_4]^{=}$ ion (4·4 B.M.) indicates three unpaired electrons and hence a tetrahedral arrangement. The magnetic moment of the $[CoCl_4]^{=}$ ion was measured earlier by Barkworth and Sugden (Barkworth, Ph.D. thesis, University of London, 1937, p. 53) using the compound $[QH]_2[CoCl_4]$, where Q = quinoline, and these workers reported the value of 4·57 B.M.

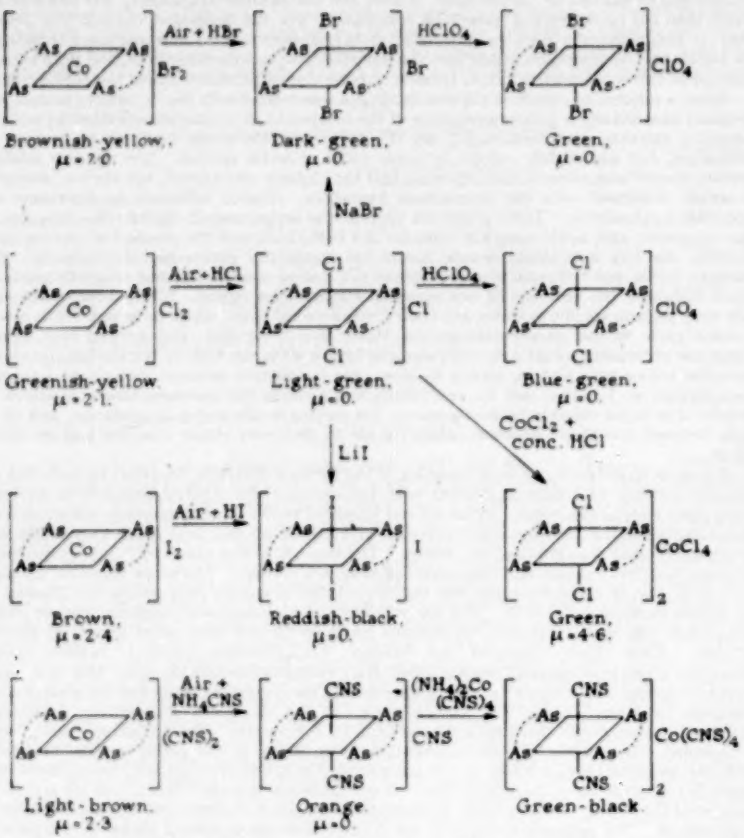
The compound dichlorodi-(*o*-phenylenebisdimethylarsine)cobalt(III) chloride, $[CoCl_2(Diarsine)_2]Cl$, is produced when the bivalent cobalt complex is oxidised in the absence of cobaltous chloride, but the product usually contains some of the less soluble $[CoCl_4]^{=}$ compound because some decomposition of the cobaltous salt occurs with the formation of cobalt chloride. The

TABLE II.

Experimental magnetic susceptibilities of some cobalt complexes.

A = *o*-Phenylenebisdimethylarsine.

Compound.	χ_M (20°), $\times 10^6$.	Diamagnetic correction, $\times 10^6$.	χ_M (corrected for for diamagnetism), $\times 10^6$.	Magnetic moment (mean μ per cobalt atom), B.M.
(1) $[CoCl_2A_2][CoCl_4]$	7820	1200	8700	2·7
(2) $[CoCl_2A_2]ClO_4$	−400	—	—	0·0
(3) $[CoCl_2A_2]^+$	−370	—	—	0·0
(4) $[CoCl_4]^=$	8260	94	8350	4·4



diamagnetic monochloride was obtained free from the $[CoCl_4]^=$ compound by making use of the solubility of the former in a mixture of chloroform and alcohol.

When the cobaltous bromide complex was heated in air with hydrobromic acid in boiling alcoholic solution the octahedral complex $[CoBr_2(Diarsine)_2]Br$ was obtained. This compound, which is deep green, is diamagnetic like the chloride but is less soluble in alcohol. The compound

was also prepared by the action of sodium bromide on the chloride complex. No complex with the $[CoBr_4]^-$ anion was obtained. The corresponding reddish-black tervalent iodide, $[CoI_2(Diarsine)_2]I$, was obtained by oxidising the cobaltous iodide complex with air in the presence of hydriodic acid. This compound was conveniently prepared by treating the chloride with a suitable iodide in alcohol; like the chloride and bromide it is diamagnetic. The thiocyanate complexes of tervalent cobalt were also investigated. A deeply coloured paramagnetic compound containing the $[Co(CNS)_4]^-$ ion was obtained when the bivalent complex was oxidised in the presence of cobaltous thiocyanate; this has a constitution similar to that of the tetrachlorocobalt(II) complex, and has the formula $[Co(CNS)_2(Diarsine)_2]_2[Co(CNS)_4]$. By treating this substance with perchloric acid the orange perchlorate $[Co(CNS)_2(Diarsine)_2]ClO_4$ was obtained, and this showed the expected diamagnetism. Aerial oxidation of the bivalent thiocyanate complexes takes place extremely readily even in cold alcoholic solution.

The most noteworthy property of these complexes is the very marked increase in stability in passing from the bivalent to the tervalent state; the stability of these complexes of tervalent cobalt is of special interest because the metal atom is co-ordinated with atoms of fairly low electronegativity. Pauling (*op. cit.*, p. 257) has pointed out that the atoms and groups which occur in the octahedral complexes of tervalent cobalt are in the main strongly electronegative, and instances the fact that chlorine in introduced more readily than iodine. In the tervalent iodide complex described here there are four arsenic and two iodine atoms attached to the cobalt, and all of these are of much lower electronegativity than atoms such as nitrogen or oxygen. The fact that this complex is quite stable, although it contains a metal in a high valency state attached to easily oxidisable groups like tertiary arsines and the iodide ion, emphasises the strength of the bonds. All of these tervalent complexes must be heated with silver nitrate and concentrated nitric acid for some hours to remove the halogen from the cation. Although compounds containing one iodine atom attached to a cobaltic atom are known, *e.g.*, $[Co(NH_3)_5I]X_2$ (where X = a univalent anion) (J. W. Mellor, "Comprehensive Treatise on Inorganic Chemistry," 1935, Vol. IX, p. 695), the compound $[CoI_2(Diarsine)_2]I$ is one of the few cobaltic complexes known in which two iodine atoms are attached to the cobalt atom. Unlike Fe^{II} and Ni^{II} derivatives, no octahedral complexes of bivalent cobalt were isolated.

The compounds prepared in this investigation and the relations between them are shown in the figure. In the tervalent complexes the two halogen atoms in the cation are shown as *trans*, but as with the corresponding tervalent compounds of iron, rhodium, and nickel it must remain speculative until proved by *X*-ray crystallography or until the *cis*-arrangement is established by optical resolution.

TABLE III.

Complex salts formed by iron, cobalt, and nickel with a di(tertiary arsine).

A = *o*-Phenylenebisdimethylarsine.

Iron.	Cobalt.	Nickel.
Bivalent $[FeA_2X_2]^0$. X = Br, I, CNS; non-electrolytes, diamagnetic, $\mu = 0$, covalent d^2sp^3 bonds. *Octahedral* (six-covalent).	*Bivalent* $[CoA_2]X_2$. X = Cl, Br, I, CNS; salts, paramagnetic, $\mu = 2{\cdot}0$—$2{\cdot}4$, covalent dsp^3 bonds. *Planar* (four-covalent).	*Bivalent* $[NiA_2]X_2$. X = Cl, Br, I, CNS, ClO_4; salts, diamagnetic, $\mu = 0$, covalent dsp^3 bonds. *Planar* (four-covalent) $[NiA_2](ClO_4)_2$: diamagnetic, $\mu = 0$. *Octahedral.*
Tervalent $[FeX_2A_2][FeX_4]$. X = Cl, Br; paramagnetic, $\mu = 2{\cdot}3$ for cation and $\mu = 5{\cdot}9$ for anion. $[FeCl_2A_2]ClO_4$. Paramagnetic, $\mu = 2{\cdot}3$. $[FeBr_2A_2]X$. X = Br, ClO_4, cation covalent, d^2sp^3 bonds. *Octahedral.*	*Tervalent* $[CoX_2A_2][CoX_4]$. X = Cl, CNS; paramagnetic, $\mu = 0$ for cation and $\mu = 4{\cdot}4$ for anion. $[CoX_2A_2]X$. X = Cl, Br, I, CNS, cation contains covalent d^2sp^3 bonds. *Octahedral.*	*Tervalent* $[NiX_2A_2]X$. X = Cl, Br, CNS; paramagnetic, $\mu = 1{\cdot}9$. $[NiCl_2A_2]B$. B = ClO_4, $\frac{1}{2}PtCl_6$, $\mu = 1{\cdot}9$, orbitals doubtful. *Octahedral.*

In Table III the behaviour of iron, cobalt, and nickel with this di(tertiary arsine) is compared so far as these investigations have proceeded. This chelate group provides a unique opportunity

for comparing the behaviour of these three metals because they form stable complexes with this diarsine in both the bivalent and tervalent states. The bonds were in all cases covalent but no unusual co-ordination numbers were observed. In the bivalent state iron forms solely octahedral complexes; the iodide and bromide are stable in air, but the chloride undergoes aerial oxidation very readily. Bivalent cobalt and nickel both form square four-covalent complexes but in addition nickel gives rise to an octahedral complex. The reluctance of bivalent cobalt to form octahedral complexes with covalent bonds is well known and towards this chelate group the ease with which these three metals form such compounds is Fe > Ni ⫸ Co; this order has also been observed with other co-ordinating groups, *e.g.*, dipyridyl.

In the tervalent state all of these elements give octahedral covalent complexes of marked stability, the cobaltic complexes containing particularly strong bonds.

This chelate group also co-ordinates readily with univalent copper, and complexes with the formulæ $[Cu(Diarsine)_2]X$ and $[CuX,Diarsine]_2$ have been prepared, where X = Cl, Br, I. This work, in collaboration with Mr. A. Kabesh, will be described in Part VII of this series.

Experimental.

Di-(o-phenylenebisdimethylarsine)cobalt(II) *Chloride*.—Cobalt chloride hexahydrate (1·2 g.) in alcohol (20 ml.) was treated with *o*-phenylenebisdimethylarsine (1·4 g.) in alcohol (40 ml.), and the solution well shaken. A greenish-yellow powder was precipitated immediately and after being heated on the water-bath for a few minutes the mixture was cooled and filtered. The *chloride* (1·3 g.) was well washed with cold alcohol, in which it was slightly soluble, and dried in a vacuum-desiccator (Found: C, 33·9; H, 4·6; Cl, 10·1. $C_{20}H_{32}Cl_2As_4Co$ requires C, 34·2; H, 4·55; Cl, 10·1%). The compound dissolved in hot water to an orange-brown solution, some decomposition occurring as was shown by the odour of the diarsine. It was also soluble to some extent in alcohol, and treatment of the alcoholic solution with silver nitrate gave a precipitate of silver chloride at once. The compound was insoluble in benzene or chloroform. When left in the air in a moist condition the compound turned green on the surface owing to oxidation. Unless tightly stoppered it developed the odour of the diarsine fairly quickly when kept owing to decomposition. Prolonged refluxing of this compound with alcoholic cobaltous chloride in carbon dioxide caused no change, but in the presence of air rapid oxidation to a cobaltic complex occurred. Magnetic susceptibility: powder form at 28·5°: $\chi = 2{\cdot}02 \times 10^{-6}$, $\chi_M = 1420 \times 10^{-6}$, correction for diamagnetism = 436×10^{-6}, whence $\mu = 2{\cdot}1$ B.M.

Di-(o-phenylenebisdimethylarsine)cobalt(II) *Bromide*.—Cobalt chloride hexahydrate (0·9 g.) and sodium bromide (4 g.) were dissolved in a mixture of alcohol (70 ml.) and distilled water (30 ml.) by heat, and the solution was treated with *o*-phenylenebisdimethylarsine (1·5 g.) in alcohol (50 ml.). The solution was well shaken. A brownish-yellow precipitate appeared immediately. After the mixture had been heated on the water-bath for a few minutes the *bromide* was filtered off and well washed with alcohol in which it was very slightly soluble. The substance (1·4 g.) was then dried in a vacuum-desiccator (Found: C, 30·7; H, 4·3; Br, 20·0. $C_{20}H_{32}Br_2As_4Co$ requires C, 30·3; H, 4·05; Br, 20·2%). The compound was slightly soluble in hot water to a brownish-orange solution which had a marked odour of the diarsine owing to hydrolysis. It was insoluble in benzene or chloroform. Magnetic susceptibility; powder form at 22°: $\chi = 1{\cdot}46 \times 10^{-6}$, $\chi_M = 1155 \times 10^{-6}$, correction for diamagnetism = 468×10^{-6}, whence $\mu = 2{\cdot}0$ B.M.

Di-(o-phenylenebisdimethylarsine)cobalt(II) *Iodide*.—Cobalt chloride hexahydrate (1·2 g.) and lithium iodide (3 g.) were dissolved in alcohol and the filtered solution was treated with *o*-phenylenebisdimethylarsine (1·5 g.) in alcohol (75 ml.). A brown precipitate was formed immediately and after the mixture had been heated on the water-bath for a few minutes the *iodide* was filtered off, well washed with alcohol, in which it was practically insoluble, and dried in a vacuum-desiccator (yield, 1·8 g.) (Found: C, 26·8; H, 3·8. $C_{20}H_{32}I_2As_4Co$ requires C, 27·1; H, 3·6%). The compound was much less soluble than the chloride or the bromide in both alcohol and water, but hot water produced the odour of the diarsine, showing that some dissolution with decomposition took place. Magnetic suceptibility: powder form at 15°: $\chi = 2{\cdot}30 \times 10^{-6}$, $\chi_M = 2040 \times 10^{-6}$, correction for diamagnetism = 490×10^{-6}, whence $\mu = 2{\cdot}4$ B.M.

Di-(o-phenylenebisdimethylarsine)cobalt(II) *Thiocyanate*.—Cobaltous chloride hexahydrate (0·7 g.) and ammonium thiocyanate (1·5 g.) were dissolved in alcohol (40 ml.) and distilled water (5 ml.), and the deep-blue solution was added to *o*-phenylenebisdimethylarsine (1·45 g.) in alcohol (40 ml.). A grey precipitate was obtained immediately, and after 5 minutes' heating on the water-bath the solution was cooled and filtered, and the residue well washed with alcohol. The filtrate was red, owing to partial oxidation to form the tervalent cobalt complex. The *thiocyanate* (1·6 g.) was dried in a vacuum-desiccator (Found: C, 34·5; H, 4·1. $C_{22}H_{32}N_2S_2As_4Co$ requires C, 35·3; H, 4·3%). The compound was insoluble in water or alcohol but in the presence of air dissolved rapidly in alcohol owing to oxidation. When preparing this compound it was difficult to avoid the formation of some of the compound $[Co(Diarsine)_2][Co(CNS)_4]$, and the presence of a small amount of this subatance is suggested by the analysis. Magnetic susceptibility: powder form at 20°: $\chi = 2{\cdot}34 \times 10^{-6}$, $\chi_M = 1740 \times 10^{-6}$, correction for diamagnetism = 450×10^{-6}, whence $\mu = 2{\cdot}3$ B.M.

Bis[dichlorodi-(o-phenylenebisdimethylarsine)cobalt(III)*]tetrachlorocobalt*(II).—The cobaltous chloride complex, $[Co(Diarsine)_2]Cl_2$ (2·0 g.), was added to a filtered solution of cobaltous chloride hexahydrate (0·9 g.) in alcohol (210 ml.) containing 10*N*-hydrochloric acid (5 ml.). The solution was then heated under reflux, filtered air being brought into contact with the surface of the solution. After about 1 hour green crystals began to form, and the cobaltous complex gradually dissolved. After about 4 hours all

of the cobaltous salt had been oxidised to give a deep-green solution. This was then filtered hot, and on cooling green crystals (2·2 g.) of the required *compound* were obtained (Found: C, 29·8; H, 3·9; Cl, 17·8; Co, 10·9. $C_{36}H_{44}Cl_2As_4Co_3$ requires C, 29·9; H, 4·0; Cl, 17·7; Co, 11·0%). The compound could be recrystallised from alcohol containing a little hydrochloric acid and cobaltous chloride; in the absence of these, some formation of the more soluble monochloride occurred. As expected from the formula, potentiometric titrations with silver nitrate and a silver electrode showed that half of the total chlorine was ionised. The compound was insoluble in water, but dissolved in a large volume of alcohol, but in this solvent it was very much less soluble than the monochloride. Magnetic susceptibility: powder form at 24°: $\chi = 4{\cdot}63 \times 10^{-6}$, $\chi_M = 7440 \times 10^{-6}$, correction for diamagnetism = 1200×10^{-6}, whence mean μ per Co atom = 2·7 B.M., and μ for one Co atom (in the $[CoCl_4]^-$ anion) = 4·6 B.M.

Dichlorodi-(o-phenylenebisdimethylarsine)cobalt(III) *Chloride*.—This compound is obtained in alcoholic solution contaminated with the above tetrachlorocobalt(II) compound by aerial oxidation under reflux of the bivalent salt $[Co(Diarsine)_2]Cl_2$ in the presence of a little hydrochloric acid. Some decomposition of the cobaltous salt gives rise to some cobaltous chloride which forms the complex anion. The substance was prepared more conveniently from the tetrachlorocobalt(II) compound as follows.

The compound $[CoCl_2(Diarsine)_2]_2[CoCl_4]$ (1·6 g.), containing a little of the monochloride, was dissolved in alcohol (250 ml.) by heat, water (100 ml.) containing 10N-hydrochloric acid (2 ml.) added, and the cooled solution shaken immediately with chloroform (250 ml.) in a separating funnel. The extraction was repeated twice. The chloroform solution was filtered, concentrated to about 75 ml., and treated with light petroleum at the b. p. until just cloudy. On cooling, beautiful bright green needles of the required *chloride* (0·9 g.) were obtained (Found: C, 31·9; H, 4·4; Cl, 14·7; Co, 8·0. $C_{36}H_{88}Cl_3As_4Co$ requires C, 32·5; H, 4·3; Cl, 14·5; Co, 8·0%). The compound was very soluble in alcohol, slightly soluble in water, and soluble in chloroform containing a little alcohol. The alcoholic solution reacted instantly with silver nitrate solution to give a precipitate of silver chloride, but the solution remained green because the chlorine in the cation did not react. Magnetic susceptibility: powder form at 14·5°: $\chi = -0{\cdot}40 \times 10^{-6}$, whence $\mu = 0$.

Dichlorodi-(o-phenylenebisdimethylarsine)cobalt(III) *Perchlorate*.—The tetrachlorocobalt(II) compound, $[CoCl_2(Diarsine)_2]_2[CoCl_4]$ (0·7 g.), was dissolved in alcohol (50 ml.) and, after it had cooled, 30% perchloric acid was added in considerable excess. A beautiful greenish-blue precipitate was obtained immediately; this was filtered off and washed many times with alcohol, in which it was insoluble (0·6 g.) (Found: C, 30·2; H, 4·0. $C_{36}H_{92}O_4Cl_3As_4Co$ requires C, 30·0; H, 4·0%). The *compound* was insoluble in water and other solvents. On heating it exploded above 300°. Magnetic susceptibility: powder form at 19°: $\chi = -0{\cdot}50 \times 10^{-6}$, whence $\mu = 0$.

Dibromodi-(o-phenylenebisdimethylarsine)cobalt(III) *Bromide*.—The cobaltous bromide complex, $[Co(Diarsine)_2]Br_2$ (1·2 g.), was added to alcohol (125 ml.) containing 48% hydrobromic acid (5 ml.), and the solution refluxed for several hours with free access of filtered air to the surface of the solution. The cobaltous salt, which was initially in suspension, gradually dissolved to form a deep-green solution. A green compound began to crystallise from the solution after about 1 hour; at the end of 12 hours all the cobaltous salt had disappeared and the flask contained a mixture of green crystals and a deep-green solution. The hot solution was then filtered, the green crystals were dissolved in hot alcohol (125 ml.), and the solution was filtered and added to the first filtrate. The whole solution was then concentrated on the steam-bath to half its bulk and allowed to cool. Dark green flat rhombs of the required *bromide* (0·2 g.) crystallised on cooling (Found: C, 27·8; H, 4·1; Br, 27·4; Co, 6·85. $C_{36}H_{92}Br_2As_4Co$ requires C, 27·5; H, 3·7; Br, 27·5; Co, 6·75%). The compound was readily soluble in alcohol but insoluble in water; it dissolved in chloroform containing a little alcohol. The alcoholic solution reacted instantly with silver nitrate to precipitate only the anionic bromine, for the solution remained green. The two covalently bound bromine atoms in the cation could be made to react with silver nitrate only by prolonged heating in the presence of concentrated nitric acid. Magnetic susceptibility: powder form at 20°: $\chi = -0{\cdot}40 \times 10^{-6}$, whence $\mu = 0$.

Dibromodi-(o-phenylenebisdimethylarsine)cobalt(III) *Perchlorate*.—The mother-liquors from the recrystallisation of the monobromide, $[CoBr_2(Diarsine)_2]Br$, were treated with an excess of 30% perchloric acid, and the light green precipitate of *perchlorate* which formed immediately was filtered off and washed several times with alcohol, in which it was insoluble. It (0·25 g.) was washed finally with water and dried in a vacuum-desiccator (Found: C, 27·2; H, 3·8. $C_{36}H_{92}O_4ClBr_2As_4Co$ requires C, 27·0; H, 3·6%). When heated, the compound exploded above 300°. Magnetic susceptibility: powder form: from the diamagnetism, $\mu = 0$.

Di-iododi-(o-phenylenebisdimethylarsine)cobalt(III) *Iodide*.—This compound was prepared by two methods each leading to the same product. The first of these is preferable since the second involves a reaction which starts with one insoluble compound and finishes with another, the purification of which is difficult.

The cobaltic monochloride complex, $[CoCl_2(Diarsine)_2]Cl$ (0·6 g.), was dissolved in alcohol (100 ml.), and the solution filtered and treated with lithium iodide (4 g.) in warm alcohol (25 ml.). The solution was heated under reflux, the colour slowly changing from green through violet to dark red. A black crystalline precipitate was formed and after 1 hour the solution was cooled and the black crystalline *complex* (0·8 g.) was filtered off and well washed with alcohol (Found: C, 23·9; H, 3·4; Co, 5·8. $C_{36}H_{88}I_2As_4Co$ requires C, 23·75; H, 3·4; Co, 5·8%).

The second method of preparation involved the aerial oxidation of the cobaltous complex in the presence of hydriodic acid. Cobalt chloride hexahydrate (0·7 g.) and lithium iodide (5 g.) were dissolved in alcohol (120 ml.), and the solution was filtered and treated with *o*-phenylenebisdimethylarsine (1·5 g.) in alcohol (30 ml.). A brown precipitate of the cobaltous complex appeared at once; to the

solution was then added 57% hydriodic acid (3 ml.), and the solution was heated under reflux with free access of air to the surface of the solution. After 3 days all of the light brown cobaltous salt had been replaced by a black precipitate (in a violet solution). The solution was cooled and filtered and the residue recrystallised from a large volume of alcohol (yield, 2·4 g.).

Under the microscope the compound consists of very dark red hexagonal crystals which are almost black by reflected light. The compound was much less soluble than the chloride or bromide in alcohol. It was slightly soluble in alcohol and in chloroform containing a little alcohol, but was insoluble in water. Magnetic susceptibility : powder form at 21° : $\chi = -0{\cdot}45 \times 10^{-6}$, whence $\mu = 0$.

Bis[dithiocyanatodi-(o-phenylenebisdimethylarsine)cobalt(III)]tetrathiocyanatocobaltate(II).—This compound was prepared after unsuccessful attempts to obtain the compound $[Co(CNS)_2(Diarsine)]$.

Cobaltous chloride hexahydrate (0·16 g.) and ammonium thiocyanate (0·16 g.) were dissolved in alcohol (40 ml.) and distilled water (5 ml.), and the solution was added to the compound $[Co(Diarsine)_2](CNS)_2$ (0·5 g.) in a 100-ml. flask. Carbon dioxide was then passed in, to exclude air, and the solution refluxed for 1 hour. Vigorous bumping occurred throughout, but no obvious change took place either in the solution or the insoluble bis(diarsine) complex. The solution was cooled, but no change had occurred. Air was then bubbled through the solution, and refluxing continued. Oxidation occurred rapidly, and after 1 hour the brown amorphous cobaltous salt had been converted into dark blue crystals (in a deep blue solution). On cooling, more greenish-black crystals separated. These (0·25 g.) were filtered off and washed with alcohol and dried in a vacuum-desiccator (Found : C, 32·4; H, 3·7. $C_{16}H_{32}N_2S_4As_4Co_3$ requires C, 32·3; H, 3·6%). Magnetic susceptibility : The *compound* was shown to be paramagnetic, owing to the $[Co(CNS)_4]^=$ anion, but the amount did not permit of an exact determination of the susceptibility.

The compound was insoluble in alcohol and water but dissolved readily in acetone to give a violet-green solution which reacted instantly with silver nitrate, leaving a pink solution of the nitrate of the complex salt.

Dithiocyanatodi-(o-phenylenebisdimethylarsine)cobalt(III) Perchlorate.—The above tetrathiocyanatocobalt(II) compound (0·2 g.) was dissolved in acetone (20 ml.) diluted with distilled water (20 ml.), and excess of perchloric acid added. Distilled water (50 ml.) was then added with stirring, giving an orange precipitate of the *perchlorate* (0·15 g.) in an almost colourless solution (Found : C, 31·7; H, 3·7; N, 3·2; Cl, 4·5. $C_{18}H_{32}O_4N_2ClS_2Co$ requires C, 31·2; H, 3·8; N, 3·3; Cl, 4·2%). The compound was diamagnetic, whence $\mu = 0$.

The magnetic measurements on the compounds described in this and the preceding paper were carried out as described in Part III (*J.*, 1950, 851).

This work was carried out during the tenure of an Imperial Chemical Industries Fellowship awarded by the University of London. The author is indebted to Professor C. K. Ingold, F.R.S., for his continued interest in this work.

Sir William Ramsay and Ralph Forster Laboratories,
University College, London, W.C.1. [*Received, March 9th*, 1950.]

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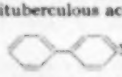
424. *The Chemotherapy of Tuberculosis. Part II. Some N-Substituted p-Phenylbenzamidines.*

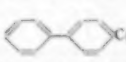
By L. Bauer and J. Cymerman.

In order to obtain isomers of the substituted *N*-4-diphenylylamidines (I) (Part I, *J.*, 1950, 1826) which, whilst possessing similar lipoid solubilities and basic strengths, are devoid of the *p*-aminobenzoic acid skeleton present in (I), a series of *N*-substituted *p*-phenylbenzamidines (II) has been prepared by interaction of 4-cyanodiphenyl and the arylsulphonates of a number of aliphatic, aromatic, and alicyclic amines. Two closely-related cyclic amidines, 2-4′-diphenylyl-4 : 5-dihydroglyoxaline and 2-4′-diphenylylbenziminazole have also been prepared.

In order to increase the lipoid solubility and basic strength of 4-aminodiphenyl, a substance of known antituberculous activity (Erlenmeyer, Becker, Sorkin, Bloch, and Suter, *Helv. Chim. Acta*, 1947, **30**, 2058), a series of substituted *N*-4-diphenylylamidines (I) was prepared (Part I, *J.*, 1950, 1826) so that the correlation between physico-chemical properties and bacteriological activity might be examined. Activity was found to vary with structure, and will be discussed in full elsewhere.

It will be seen that the *N*-4-diphenylylamidines (I) possess the *p*-aminobenzoic acid skeleton, the presence of which has been claimed by a number of workers (cf. Erlenmeyer *et al.*, *loc. cit.*) to enhance antituberculous activity.

(I.) 

 (II.)

Thus Erlenmeyer *et al.* (*loc. cit.*) examined *p*-aminobenzoic acid and its *n*-alkyl esters (methyl—*n*-heptyl) whilst *p*-aminobenzamidine and 2-*p*-aminophenylpropene were prepared and tested

by Erlenmeyer, Noll, and Sorkin (*Helv. Chim. Acta*, 1949, **32**, 1676). Other compounds possessing the *p*-aminobenzoic acid structure, and found active *in vitro*, include 4-aminodiphenyl and its isostere 2-*p*-aminophenylpyridine (Erlenmeyer *et al.*, *loc. cit.*), 4-aminosalicylic acid (Lehmann, *Lancet*, 1946, 15), and 2-naphthylamine (Bloch, Lehr, and Erlenmeyer, *Helv. Chim. Acta*, 1945, **28**, 1406).

In order to test whether the presence of this structure has any beneficial effect on antituberculous activity, the synthesis of a series of *N*-substituted *p*-phenylbenzamidines (II) was undertaken, and forms the subject of this communication. In these compounds, which do not possess the *p*-aminobenzoic acid skeleton, physical properties such as lipoid solubility and basic strength must approach closely to those of the isomeric *N*-4-diphenylylamidines (I), and a comparison of their bacteriological activities should therefore afford some evidence regarding the effect of the presence or absence of the *p*-aminobenzoic acid residue.

p-Phenylbenzamidine and the following *N*-substituted phenylbenzamidines were prepared by Oxley and Short's method (*J.*, 1947, 147) from 4-cyanodiphenyl and the arylsulphonates of a series of aliphatic, aromatic, and alicyclic amines: *N*-*n*-butyl-, *N*-*cyclo*hexyl-, *N*-phenyl-, *N*-*p*′-chlorophenyl-, *N*-*p*′-ethoxyphenyl-, *N*-*p*′-butoxyphenyl-, *N*-4-diphenylyl-, and *N*-*p*′-piperidinophenyl-. 4-Cyanodiphenyl was obtained in good yield by thermal decomposition *in vacuo* of the copper complex obtained by the action of potassium cuprocyanide on diazotised 4-aminodiphenyl, the cyanide distilling as formed. Reaction between the amine arylsulphonates and the cyanide took place at temperatures between 180° and 270° and required from 0·75 to 7 hours' heating. The yields ranged from 18 to 95%. The bases obtained were characterised as their benzenesulphonates, hydrochlorides, picrates, or toluene-*p*-sulphonates.

To examine the effect of additional cyclisation of the *p*-phenylbenzamidine molecule (II), the corresponding dihydroglyoxaline, 2-4′-diphenylyl-4 : 5-dihydroglyoxaline was prepared in excellent yield from 4-cyanodiphenyl and ethylenediamine by the method outlined by Oxley and Short (*J.*, 1947, 500). Reaction of the cyanide with *o*-phenylenediamine by Holljes and Wagner's method (*J. Org. Chem.*, 1944, **9**, 31) gave 2-4′-diphenylylbenziminazole, an analogue of (II; R = Ph) from which it differs by only two hydrogen atoms. Results of bacteriological and other examinations of these compounds will be reported elsewhere.

Experimental.

4-Cyanodiphenyl.—A hot solution of 4-aminodiphenyl (18·6 g.) in water (400 c.c.) containing hydrochloric acid (10 c.c.; 10N.) was poured on ice (200 g.). The stirred suspension of the hydrochloride was cooled to 5° and treated successively with hydrochloric acid (24 c.c.; 10N.) and sodium nitrite (8·6 g.) in water (20 c.c.). Sodium carbonate was added until the diazo-solution was almost neutral, whereupon it was slowly added to a solution of potassium cuprocyanide [from potassium cyanide (30 g.) in water (50 c.c.) and copper sulphate (26·6 g.) in warm water (100 c.c.)] at 60—70°. Nitrogen was evolved and a brown complex precipitated which was filtered off, washed, dried, and distilled under reduced pressure; 4-cyanodiphenyl (9·8 g., 50%) distilled at 120—140°/0·05 mm., solidifying to a solid, m. p. 80—82°. Recrystallisation from light petroleum (b. p. 60—80°) gave crystals, m. p. 85—86° (Dobner, *Annalen*, 1874, **172**, 111, gives m. p. 84—85°).

p-*Phenylbenzamidine.*—A mixture of 4-cyanodiphenyl (2·5 g.) and ammonium benzenesulphonate (5 g., 2 mol.) was fused at 270° (bath temp.) for 3 hours. Trituration of the cooled melt with acetone, and crystallisation from aqueous alcohol gave the *benzenesulphonate* (2·9 g., 59%) crystallising from water in plates, m. p. 285° (Found: N, 7·6, 7·6. $C_{19}H_{18}N_2,C_6H_6O_3S$ requires N, 7·9%). A similar fusion at 250° for 4 hours gave only 35% of the salt. The *amidine* separated from chloroform–light petroleum (b. p. 40—70°) in plates, m. p. 171—172° (Found: N, 14·3. $C_{13}H_{12}N_2$ requires N, 14·3%). The *picrate* formed yellow needles, m. p. 211—212°, from aqueous alcohol. It retained water of crystallisation even after being dried at 115° (Found: N, 15·15, 15·3, 15·25. $C_{19}H_{18}N_2,C_6H_3O_7N_3,2H_2O$ requires N, 15·2%). The *hydrochloride* crystallised from dilute hydrochloric acid (1 : 1) in plates, m. p. 235—239°, which also retained water of crystallisation even after being dried at 135° (Found: C, 61·9; H, 5·9; N, 11·2, 11·0, 11·2. $C_{19}H_{18}N_2,HCl,H_2O$ requires C, 62·2; H, 6·0; N, 11·2%).

n-*Butylammonium Benzenesulphonate.*—Prepared by mixing equivalent quantities of the amine in ether with the acid in methanol, this *salt* separated from methanol–ether in plates, m. p. 108·5° (Found: N, 6·0. $C_4H_{11}N,C_6H_6O_3S$ requires N, 6·1%).

p-*Phenyl-N-n-butylbenzamidine.*—Fusion of n-butylammonium benzenesulphonate (2 g.) and 4-cyanodiphenyl (0·9 g.) at 225° for 7 hours gave, on treatment with cold ether, unreacted cyanide (0·6 g.). The residue on crystallisation from water afforded plates of the *benzenesulphonate* (0·2 g., 29% calculated on recovered cyanide), m. p. 164—165° (Found: N, 6·7. $C_{17}H_{20}N_2,C_6H_6O_3S$ requires N, 6·8%). A similar fusion at 255° for 2 hours gave 12% of the benzenesulphonate. The *hydrochloride* separated from hydrochloric acid (1 : 1) in plates, m. p. 220—221° (Found: N, 9·8. $C_{17}H_{20}N_2,HCl$ requires N, 9·7%).

cyclo*Hexylammonium Benzenesulphonate.*—This *salt* crystallised in needles, m. p. 213°, from alcohol–ether (Found: N, 5·6. $C_6H_{13}N,C_6H_6O_3S$ requires N, 5·5%).

N-cyclo*Hexyl*-p-*phenylbenzamidine*.—A mixture of 4-cyanodiphenyl (1·8 g.) and *cyclo*hexylammonium benzenesulphonate (5 g.) was heated at 220° for 6 hours. The crude benzenesulphonate (0·8 g., 18%) was converted into the *hydrochloride*, which crystallised from hydrochloric acid (1 : 1) in prisms, m. p. 267—269° (decomp.) (Found : N, 9·2. $C_{19}H_{22}N_2$,HCl requires N, 8·9%). The *amidine* crystallised in prisms, m. p. 131·5°, from light petroleum (b. p. 60—90°) (Found : N, 9·9. $C_{19}H_{22}N_2$ requires N, 10·1%).

N : p-*Diphenylbenzamidine*.—Anilinium benzenesulphonate (1·9 g.) and 4-cyanodiphenyl (1 g.) were heated at 210° for 5 hours. Extraction with boiling water gave the *benzenesulphonate* (2 g., 83%) in plates, m. p. 191—192° (Found : N, 6·7. $C_{19}H_{16}N_2.C_6H_6O_3S$ requires N, 6·5%). The *amidine* crystallised in rhombs, m. p. 175·5°, from chloroform–light petroleum (b. p. 40—70°) (Found : N, 10·2. $C_{19}H_{16}N_2$ requires N, 10·3%).

p-*Phenyl*-N-p′-*chlorophenylbenzamidine*.—Fusion of 4-cyanodiphenyl (2·2 g.) and *p*′-chloroanilinium toluene-*p*-sulphonate (4·5 g.) at 200° for 1 hour gave the *toluene*-p-*sulphonate* (5·6 g., 95%) crystallising as plates, m. p. 270° (decomp.), from water (Found : N, 5·85. $C_{19}H_{15}N_2Cl.C_7H_8O_3S$ requires N, 5·85%). The *amidine* formed plates, m. p. 202°, from chloroform–light petroleum (Found : N, 9·25. $C_{19}H_{15}N_2Cl$ requires N, 9·15%).

p-*Phenyl*-N-p′-*ethoxyphenylbenzamidine*.—*p*-Ethoxyanilinium benzenesulphonate (3 g.) and 4-cyanodiphenyl (1·8 g.) reacted at 180° for 2·75 hours by which time the reaction mixture had solidified. Trituration with acetone gave the pure *benzenesulphonate* (3·8 g., 80%), m. p. 222—224°, unchanged on recrystallisation from water (Found : N, 6·2. $C_{21}H_{20}ON_2.C_6H_6O_3S$ requires N, 5·9%). The *amidine* crystallised from chloroform–light petroleum in plates, m. p. 206—207° (Found : N, 9·2. $C_{21}H_{20}ON_2$ requires N, 8·9%). The *hydrochloride* consisted of flat needles, m. p. 256—257° (Found : N, 7·9. $C_{21}H_{20}ON_2$,HCl requires N, 7·9%).

p-n-*Butoxyphenylammonium Benzenesulphonate*.—This *salt* separated from methanol–ether in stout needles, m. p. 186—187° (Found : N, 4·5. $C_{16}H_{19}ON.C_6H_6O_3S$ requires N, 4·3%).

p-*Phenyl*-N-p′-n-*butoxyphenylbenzamidine*.—Reaction of 4-cyanodiphenyl (1·8 g.) with *p*-n-butoxyphenylammonium benzenesulphonate (1·6 g.) at 180° for 4 hours gave the *benzenesulphonate* (49%) crystallising from water in colourless needles, m. p. 188° (Found : N, 5·8. $C_{23}H_{24}ON_2.C_6H_6O_3S$ requires N, 5·6%). The *amidine* crystallised from chloroform–light petroleum in rhombs, m. p. 212—213° (Found : N, 8·3. $C_{23}H_{24}ON_2$ requires N, 8·1%).

p-*Phenyl*-N-4-*diphenylylbenzamidine*.—A mixture of 4-cyanodiphenyl (1 g.) and 4-diphenylylammonium benzenesulphonate (2 g.) (Bauer and Cymerman, *J.*, 1950, 1826) was heated at 250—255° for 3 hours. After trituration with acetone, the *benzenesulphonate* (1·6 g., 57%) recrystallised from aqueous methanol in cream needles, m. p. 246—247° (Found : N, 5·3. $C_{25}H_{20}N_2.C_6H_6O_3S$ requires N, 5·5%). The *amidine* formed colourless plates, m. p. 283—284°, from 2-ethoxyethanol (Found : N, 8·3. $C_{25}H_{20}N_2$ requires N, 8·0%).

p-*Piperidinophenylammonium Ditoluene*-p-*sulphonate*.—Prepared from *p*-piperidinoaniline, b. p. 125—130°/0·05 mm., n_D^{20} 1·5980, the *ditoluene*-p-*sulphonate* separated in rhombs, m. p. 192—193°, from methanol–ether (Found : N, 5·5. $C_{11}H_{16}N_2.2C_7H_8O_3S$ requires N, 5·4%). The dihydrochloride separated from alcohol–ether in flat needles, m. p. 227—228° (decomp.) (sealed tube) (Found : N, 11·2. Calc. for $C_{11}H_{16}N_2$,2HCl : N, 11·2%). Leppla (*Ber.*, 1888, **21**, 2285) reports a hydrochloride monohydrate; no m. p. is given.

p-*Phenyl*-N-p′-*piperidinophenylbenzamidine*.—The melt obtained by fusion of cyanodiphenyl (1·8 g.) and *p*-piperidinophenylammonium ditoluene-*p*-sulphonate (7·5 g.) at 200° for 0·75 hours was cooled and dissolved in methanol, and the solution was basified with cold methanolic potassium hydroxide. The crude amidine was dissolved in dilute hydrochloric acid (200 c.c.; 2·5N.), the solution filtered and extracted with ether, and the base liberated at 0°; the *amidine* crystallised from ligroin (b. p. 96—100°) or alcohol as clusters of needles, m. p. 207° (decomp.) (Found : N, 11·9. $C_{24}H_{23}N_3$ requires N, 11·8%). The *dihydrochloride* separated from alcohol–ether in buff rhombs, m. p. 260° (decomp.) (Found : N, 9·8. $C_{24}H_{23}N_3$,2HCl requires N, 9·8%).

2-4′-*Diphenylyl*-4 : 5-*dihydroglyoxaline*.—Reaction of 4-cyanodiphenyl (1·8 g.) with ethylenediamine ditoluene-*p*-sulphonate (8·1 g., 2 mols.) and ethylenediamine (1·2 g.) at 200° for 5·5 hours gave the *toluene*-p-*sulphonate* (3·75 g., 95%), crystallising from water in colourless plates, m. p. 261—262° (Found : N, 7·0. $C_{15}H_{14}N_2.C_7H_8O_3S$ requires N, 7·1%). The *base* formed needles, m. p. 198°, from chloroform–light petroleum (Found : N, 12·6. $C_{15}H_{14}N_2$ requires N, 12·6%).

2-4′-*Diphenylylbenziminazole*.—A mixture of 4-cyanodiphenyl (2 g.) and *o*-phenylenediamine dihydrochloride (1·8 g.) was heated at 200° (bath temp.) for 2 hours. The cooled melt was triturated with ether, and the residue extracted with boiling water (500 c.c.) and filtered. The residue (0·9 g., 30%) crystallised from *iso*propanol–ether in white rhombic plates, m. p. 316—317°, of 2-4′-*diphenylylbenziminazole hydrochloride* (Found : N, 9·2. $C_{19}H_{14}N_2$,HCl requires N, 9·15%). The aqueous filtrate was basified at 0° with concentrated ammonia solution giving the *base* (0·6 g., 22%) which crystallised from aqueous acetone in prisms, m. p. 291·5—292° (Found : N, 10·5. $C_{19}H_{14}N_2$ requires N, 10·4%).

This work was carried out under the auspices of the National Health and Medical Research Council, to whom thanks are due for financial assistance.

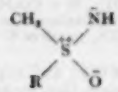
Organic Chemistry Department, University of Sydney. [*Received, April 11th*, 1950.]

425. *Dimethylsulphoximine.*

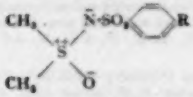
By H. R. Bentley and J. K. Whitehead.

Oxidation of dimethylsulphintoluene-*p*-sulphonylimine (VI) with permanganate followed by acid hydrolysis gives dimethylsulphoximine (I; R = CH_3). The toxic factor from nitrogen trichloride-treated proteins is considered to be a member of this new class of sulphur compounds.

The toxic factor ($C_5H_{11}O_2N_2S$) from nitrogen trichloride-treated proteins is derived from methionine by the addition to the sulphur atom of one atom each of nitrogen, oxygen, and hydrogen (Bentley, McDermott, Pace, Whitehead, and Moran, *Nature*, 1950, **165**, 150). In order to account for its considerable stability the molecule is represented formally as [I; R = ·CH_2·CH_2·$CH(NH_2)$·CO_2H] which is stabilised by resonance in the same manner as a



(I.)



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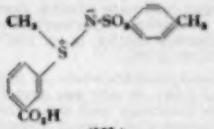
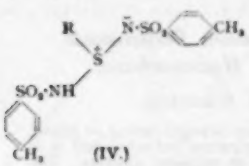


(III.)

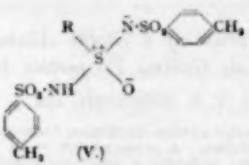
sulphone. This serves in particular to explain the considerably increased resistance to acid hydrolysis of (I) compared with the sulphilimines $R_2S{\rightarrow}NR'$ (Mann and Pope, *J.*, 1922, **121**, 1052; Tarbell and Weaver, *J. Amer. Chem. Soc.*, 1941, **63**, 2939), where resonance stabilisation of this type cannot occur.

Compounds of the type (I) have not previously been described although it is logical to expect them to arise by oxidation of sulphilimines. The name "sulphoximine" is adopted for the class of compound; • the toxic factor from nitrogen trichloride-treated proteins may be designated "methionine-sulphoximine."

The present communication describes the synthesis of dimethylsulphoximine (I; R = CH_3).•



(IV.)



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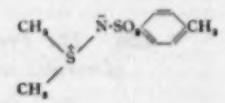

(VI.)

Clark, Kenyon, and Phillips (*J.*, 1927, 188) attempted the oxidation of (III) with perhydrol but obtained only toluene-*p*-sulphonamide and the corresponding sulphone. The compounds (IV; R = C_6H_5, C_7H_8), which are stable to hydrogen peroxide, can be oxidised to (V; R = C_6H_5, C_7H_8) by means of alkaline permanganate (*idem*, *ibid.*, 1930, 1225). In the present case, dimethylsulphintoluene-*p*-sulphonylimine (toluene-*p*-sulphondimethylsulphidimide) (VI) is found to be oxidised by means of neutral or alkaline permanganate to toluene-*p*-sulphondimethylsulphoximide (II; R = CH_3); prolonged treatment with permanganate oxidises the methyl group of the toluene radical giving *p*-carboxybenzenesulphondimethylsulphoximide (II; R = CO_2H).

With concentrated sulphuric acid at room temperature overnight or on the steam-bath after 5 minutes, (II; R = CH_3) undergoes hydrolysis yielding (I; R = CH_3) as the principal product. Small quantities of dimethyl sulphone may also be formed by the second mode of hydrolysis but, if so, the amounts formed have not been sufficient for characterisation in the present case.

(I; R = CH_3) is obtained in 30—40% yield as a low-melting, hygroscopic solid. It is conveniently characterised by means of its crystalline picrate which is more easily purified than the free base.

• The name "sulphoximine" for the class of compounds typified by (I), suggested to one of the authors (H. R. B.) by Sir Robert Robinson, is an abbreviated form of "sulphoxidimine."

EXPERIMENTAL.

Toluene-p-sulphondimethylsulphorimide.—A mixture of dimethylsulphintoluene-*p*-sulphonylimine (VI) (10·0 g.) in aqueous sodium hydroxide (3% w/v; 50 ml.) and potassium permanganate (10·0 g., 1·5 mols.) in hot water (50 ml.) was heated for 5 minutes on the steam-bath. The mixture was then cooled and cleared with sulphur dioxide. The white solid was collected, washed thoroughly with water, and then stirred with aqueous sodium hydrogen carbonate (50% w/v; 100 ml.), collected, washed with water, and dried. *Toluene-p-sulphondimethylsulphorimide* (II; R = CH_3) crystallised from water as flat colourless needles, m. p. 167—169° (8·0 g., 75%) (Found: C, 43·7; H, 5·4; N, 6·0. $C_9H_{11}O_3NS_2$ requires C, 43·7; H, 5·3; N, 5·7%).

p-*Carboxybenzenesulphondimethylsulphoximide.*—A mixture of dimethylsulphintoluene-*p*-sulphonylimine (3·0 g.) and potassium permanganate (3·9 g., 2 mols.) in water (60 ml.) was boiled for 10 minutes and the mixture then cooled and cleared with sulphur dioxide. The crude dried reaction product melted over the range 160—200° and was partly soluble with effervescence in aqueous sodium hydrogen carbonate (5% w/v; 50 ml.). The insoluble fraction crystallised from water as colourless needles, m. p. 165—167° alone or mixed with a specimen of toluene-*p*-sulphondimethylsulphoximide. Acidification of the sodium hydrogen carbonate solution gave p-*carboxybenzenesulphondimethylsulphoximide* (II; R = CO_2H) as a white precipitate. This was collected, washed with water and was obtained after crystallisation from water as colourless needles, m. p. 256° (Found: C, 39·2; H, 4·1; N, 4·9. $C_9H_{11}O_4NS_2$ requires C, 39·0; H, 4·0; N, 5·1%).

Dimethylsulphoximine.—A mixture of the toluene-*p*-sulphonyl compound (16·0 g.) and sulphuric acid (*d* 1·84; 25 ml.) was heated for 5 minutes on the steam-bath, and the mixture then cooled and diluted cautiously with water (250 ml.). The solution, neutralised with sodium hydrogen carbonate, was concentrated to small volume under diminished pressure on the steam-bath, and ethanol (250 ml.) added to the residue. The ethanol solution, filtered free from salts, was again concentrated and a further quantity of salts removed similarly, the final ethanol solution being evaporated to dryness and the dry residue extracted with hot dry benzene (2 × 100 ml.). Evaporation of benzene under diminished pressure left *dimethylsulphoximine* as a pale brown oil (2·0 g., 30%) which crystallised on cooling. Redistilled, the product was obtained as a colourless oil, b. p. 130—140° (bath temp.)/15 mm., solidifying to a crystalline solid, m. p. 52—53° (Found: C, 26·4; H, 7·5; N, 13·7. C_2H_7ONS requires C, 25·8; H, 7·5; N, 15·0%). The dry product is deliquescent.

Equimolecular amounts of the free base and picric acid in water give a *picrate*, crystallising from water as long orange-yellow needles, m. p. 182—184° (Found: C, 29·5; H, 3·1; N, 16·8. $C_2H_7ONS,C_6H_3O_7N_3$ requires C, 29·8; H, 3·1; N, 17·4%).

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426. *The Preparation of a Stable Aluminium Dodecanoate (Laurate) with no Gelling Properties in Hydrocarbons.*

By J. GLAZER, T. S. MCROBERTS, and J. H. SCHULMAN.

The preparation is described of a stable aluminium dodecanoate (laurate) having no gelling properties in hydrocarbon solution. A consideration of its properties indicates that it is aluminium trilaurate; analysis indicates a small percentage of occluded alumina. The absence of gelling is attributed to the absence of intermolecular hydrogen-bond cross-links.

PREVIOUS work (McRoberts and Schulman, *Nature*, 1948, **162**, 101; *Proc. Roy. Soc., A*, Discussion on Hydrocarbon Gelling, 1949) has suggested that the gelling properties of the aluminium soaps depend upon the existence of a hydroxy-group in the molecule. It is through the agency of this group that cross-linking takes place, and the resultant hydrogen-bonded network gives rise to the observed gelling properties in hydrocarbon solvents.

Should this be so, an aluminium tri-soap, since it does not contain a hydroxy-group, should exhibit no such gelling properties. It has hitherto been impossible to test this contention since the tri-soaps cannot be prepared by any of the known methods of synthesis involving fatty acids (and their alkali-metal salts) and both inorganic aluminium salts and organic aluminium compounds of the type AlX_3, where the group X is appreciably electronegative. An attempt has now been made to prepare aluminium dodecanoate (trilaurate) by reaction of lauric acid with trimethylaluminium.

EXPERIMENTAL.

Trimethylaluminium, prepared according to the method of Pitzer and Gutowsky (*J. Amer. Chem. Soc.*, 1946, **68**, 2204), was treated with pure lauric acid (Verley) in dry benzene, in the absence of moisture and oxygen, and the product extracted by removing the benzene and any excess of trimethylaluminium by distillation. The product (A) was purified by trituration with dry light petroleum (b. p. 40—60°) until of constant m. p. 94° (Found: Al_2O_3, 10·3%). The same product, m. p. 94°, was obtained whether the reactants contained excess of lauric acid or of trimethylaluminium. It was a yellow, amorphous

powder which dissolved easily in benzene to give a highly mobile solution, no trace of gelling being noticeable. Prolonged contact of such a solution with water did not produce any gelling tendencies; yet, when the product was heated in moist acetone or dioxan, a second product (B), m. p. 180—220° (Found: Al_2O_3, 14·3%), was formed which exhibited strong gelling properties in benzene and light petroleum.

The addition of "hydrogen-bond forming" organic liquids to gels of aluminium dilaurate in benzene and light petroleum destroyed the gel structure and produced mobility. The following liquids were effective: acetone, di*iso*propyl ketone, ether, methanol, and ethanol.

Discussion.

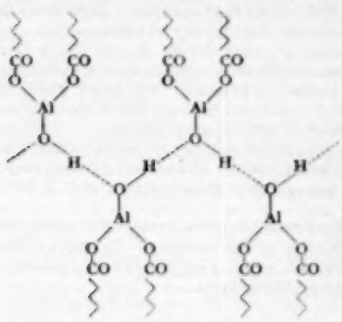
The absence of gelling properties shown by A and the strong gelling shown by B suggests that the former is the tri- and the latter the di-soap. It is known that the di-soap is a strong gelling agent in hydrocarbon solvents. However, the analytical results are clearly not in accord with the theoretical values expected for these compounds:

Compound.	Al_2O_3, %, found.	Al_2O_3, %, calc.
Product A	10·3	8·1 for tri-soap.
Product B	14·3	11·5 for di-soap.
Commercial di-soap	14·7	,, ,,

Product A was refluxed with light petroleum, the mixture filtered, and the resulting clear solution evaporated to dryness (Found: Al_2O_3, 9·9%).

The high aluminium content of product A may, *a priori*, be due to the presence of the di-soap or methylaluminium di-soap in appreciable amount, or a small (*ca.* 2%) occlusion of alumina. The absence of di-soaps is shown by the sharpness and constancy of the m. p. after repeated washing with solvent, and the complete lack of gelling properties. The existence of a stable methylaluminium di-soap is unlikely in view of the extreme instability of the known aluminium alkyls. For these reasons, we believe A to consist of the tri-soap containing a small amount of occluded alumina; such an impurity would not affect the sharpness or the constancy of the m. p. Should this be so, the di-soap derived (by hydrolysis) should retain the high aluminium content. This is borne out by the analytical results for the product B. The formation of visually transparent solutions by the tri-soap would indicate that the alumina is molecularly dispersed.

No hydrolysis takes place when a benzene solution of the tri-soap is kept in contact with water, the solution remaining perfectly mobile. This is in marked contrast with the di-soap alcoholates (McRoberts and Schulman, *loc. cit.*), where the hydrolysis proceeds immediately on the exposure to traces of atmospheric moisture. The tri-soap would appear to be more stable than has hitherto been thought. Under more drastic conditions, such as refluxing with aqueous acetone or dioxan, the tri- is hydrolysed to the di-soap. This hydrolysis product exhibits strong gelling properties in hydrocarbon dispersion.



The inset type of hydrogen-bond cross-linking is envisaged for aluminium di-soap gels. For a stable hydrogen bond of the type O–H . . . O, the inter-oxygen distance varies between 2·5 and 2·9 A. for different compounds. This requires that the cross-link direction, in a di-soap gel, is normal to the $R{\cdot}CO_2{-}Al{-}CO_2R$ plane, thereby allowing sufficient space in the cross-link direction to accommodate the long-chain hydrocarbon portion of the molecule. This space conception is discussed in connection with a monolayer study on the formation of metal soaps (Wolstenholme and Schulman, *Trans. Faraday Soc.*, 1950, **46**, 475). The presence of hydrogen bonds is supported by the negative streaming birefringence exhibited by hydrocarbon gels of aluminium di-soaps (O. Snellman, Uppsala, private communication).

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427. *The Isolation of Uridine and Cytidine from Yeast Ribonucleic Acid.*

By D. T. Elmore.

An improved method for the separation and isolation of uridine and cytidine from yeast ribonucleic acid is described. It has been shown that hydrolysis of yeast ribonucleic acid, using aqueous pyridine, is incomplete under the conditions used by Bredereck, Richter, and Martini (*Ber.*, 1941, **74**, 694). Appreciable deamination of cytidine occurs during the process.

The usual technique employed for the preparation of nucleosides from pentose nucleic acids is that due to Bredereck *et al.* (*Ber*, 1941, **74**, 694). Although this method affords satisfactory yields of guanosine and adenosine, and, by a suitable modification, a fair quantity of uridine also (Gulland and Smith, *J.*, 1947, 338), the isolation of cytidine has proved difficult. Thus Gulland and Smith (*J.*, 1948, 1527) were compelled to resort to the hydrolysis of cytidylic acid, and Harris and Thomas (*J.*, 1948, 1936) obtained extremely small yields of cytidine after hydrolysis of yeast ribonucleic acid with aqueous pyridine. Loring and Ploeser (*J. Biol. Chem.*, 1949, **178**, 439) have recently described a method for preparing the pyrimidine nucleosides by acid hydrolysis of yeast ribonucleic acid. Unfortunately, however, the conditions of hydrolysis employed caused considerable deamination of the cytidine.

It therefore seemed desirable to investigate more fully the degradative method of Bredereck *et al.* Some reference to this problem is made by Markham and Smith (*Nature*, 1949, **163**, 250) who state that "the hydrolysis of ribonucleic acid by pyridine–water is far from complete, and the hydrolysate contains at least seven different substances." This agrees with the observations reported herein, since hydrolysis of yeast ribonucleic acid with 50% aqueous pyridine for 103 hours removed only 57% of the total phosphorus as inorganic phosphate. Furthermore, examination of the hydrolysate by paper chromatography revealed the presence of considerable quantities of nucleotides.

A method, similar in principle to that described by Harris and Thomas (*Nature*, 1948, **161**, 931; *J.*, 1948, 1936), was employed for the separation of synthetic mixtures of cytidine and uridine (Elmore, *Nature*, 1948, **161**, 931). This has now been adapted for the isolation of these nucleosides from hydrolysates of yeast ribonucleic acid. Yields of uridine were of the same order as those reported by Harris and Thomas (*locc. cit.*). Although yields of cytidine were considerably higher than obtained by these authors, they must still be regarded as low, especially since Vischer and Chargaff (*J. Biol. Chem.*, 1948, **176**, 715) report that cytosine is three times as abundant as uracil in yeast ribonucleic acid. In agreement with Loring and Ploeser (*loc. cit.*) and contrary to the suggestion of Harris and Thomas (*J.*, 1948, 1936), it was found that destruction of cytidine did not occur to any marked extent under the conditions of acid hydrolysis which are normally employed to remove traces of purine nucleosides. The small yields of cytidine may be accounted for, however, since it has been found that deamination of the cytosine nucleoside or nucleotide occurs during the initial hydrolysis with aqueous pyridine. Cytidylic acid, when subjected to these conditions, afforded an appreciable quantity of uridine, which was detected by paper-chromatographic examination of the hydrolysate. The extent of deamination may be judged from the fact that cytidine sulphate was obtained from cytidylic acid in 68% yield.

It has been found advantageous to delay hydrolysis of residual purine nucleosides until after the separation and isolation of uridine. This modification in the procedure circumvents the difficulty of crystallization of uridine frequently encountered, which is attributed to the presence of a small amount of gummy material formed during the acid hydrolysis.

Experimental.

Preparation of Uridine.—A sample of uridine, m. p. 163—165°, was prepared from yeast ribonucleic acid by a combination of the methods of Bredereck *et al.* (*loc. cit.*) and Gulland and Hobday (*J.*, 1940, 746).

Preparation of Cytidine from Cytidylic Acid.—The method employed was that due to Gulland and Smith (*J.*, 1948, 1527). The yield was 68%, and the m. p. 228—230° (decomp.).

Preparation of "Zeo-Karb 215."—The resin was alternately crushed in an iron mortar and sieved until it passed a 30-mesh but was retained by a 40-mesh size. Before use the resin was freed from soluble polymers by subjecting it four times to the following cycle of operations: treatment with 2N-hydrochloric acid, treatment with water until the washings were neutral, treatment with sodium hydroxide, and treatment with water until the washings were neutral. The sodium hydroxide used was 0·5N. in the first two, and 0·1N. in the last two, cycles. Finally, the resin was treated with 2N-hydrochloric acid,

washed with water, and dried at room temperature. Treatment with acid or alkali was carried out in a downward direction in a column. Washing with water was carried out in the reverse direction.

Behaviour of Cytidine on "Zeo-Karb 215."—A solution (0·05M.) of cytidine (0·61 g.) in water (50 c.c.) was passed down a column (4·2 × 1·2 cm.) of "Zeo-Karb 215" (2 g.) at a rate of 1·5 c.c./min., and the percolate collected in fractions. Kjeldahl analyses of the latter demonstrated that cytidine was quantitatively retained. By determination of the "break-through point," the capacity of the resin for cytidine under these conditions was found to be 1·25 milliequivs./g. The column was eluted with 0·1N-ammonia (100 c.c.), the eluate evaporated under reduced pressure to remove ammonia (Nessler test), and the solution analysed by the Kjeldahl technique. Recovery was 81%.

Behaviour of Uridine on "Zeo-Karb 215."—In a similar experiment it was shown that uridine was not retained by a column of "Zeo-Karb 215."

Separation of a Synthetic Mixture of Cytidine and Uridine.—A solution (0·05M, with respect to each nucleoside) of cytidine (0·61 g.) and uridine (0·61 g.) in water (50 c.c.) was passed down a column (5·6 × 1·2 cm.) of "Zeo-Karb 215" (3 g.) at a rate of 0·7 c.c./min. The column was washed with water (100 c.c.), and the combined washings and filtrate were evaporated to dryness, yielding crystalline uridine (0·608 g., 99·8%), m. p. 162—165° (Found: N, 11·5. Calc. for $C_9H_{12}O_6N_2$: N, 11·5%).

The column was eluted with 0·1N-ammonia (100 c.c.), and the eluate evaporated to dryness, affording crystalline cytidine (0·433 g., 71%), m. p. 208—211° (Found: N, 17·0. Calc. for $C_9H_{13}O_5N_3$: N, 17·3%).

Preparation of Cytidine and Uridine from the Pyridine Hydrolysate of Yeast Ribonucleic Acid.—Yeast ribonucleic acid (100 g.) was hydrolysed with 50% aqueous pyridine by the method of Bredereck *et al.* (*loc. cit.*), and the guanosine and adenosine were removed as described by these authors. Yields of guanosine were 10—14 g. and of adenosine 6—11 g.

The mother-liquors were diluted to 1500 c.c. and passed down a column (28·5 × 3·0 cm.) of "Zeo-Karb 215" (90 g.) at a rate of 1·2 c.c./min. The column was washed with water (700 c.c.), and the combined percolate and washings were evaporated under reduced pressure to a syrup. After evaporation once with alcohol, the syrup solidified to a brown mass of crude uridine which was crystallized from 95% alcohol (yield, 16·65 g.). Recrystallized from 95% alcohol, it (11·95 g.) had m. p. 163·5—166° alone or on admixture with a sample of uridine prepared by the Gulland–Bredereck procedure, $[\alpha]_D^{25}$ +9·6° (*c*, 2·0 in water) (Found: C, 44·7; H, 4·7; N, 11·5. Calc. for $C_9H_{12}O_6N_2$: C, 44·3; H, 4·9; N, 11·5%).

The column was eluted with 0·1N-ammonia (5 l.) and the eluate evaporated under reduced pressure to 200 c.c. Sulphuric acid (2·2 c.c.) was added, the solution was heated under reflux for 1·5 hours and cooled, and purines were precipitated by the addition of hot silver sulphate solution. Silver purines were filtered off and washed twice with cold water, and the combined washings and filtrate evaporated under reduced pressure to 500 c.c. Silver ions were removed by hydrogen sulphide and, after aeration of the solution, barium hydroxide was added to pH 2·2—2·4. Barium sulphate was filtered off and washed with hot water, and the combined washings and filtrate were evaporated to 60 c.c. Boiling alcohol was added to the hot solution until crystallization commenced. The cytidine sulphate obtained (3·65 g.) had m. p. 224—225° (decomp.), $[\alpha]_D^{25}$ +37·5° (*c*, 1·5 in 1% aqueous sulphuric acid) [Found: C, 37·2; H, 5·13; N, 14·5. Calc. for $(C_9H_{13}O_5N_3)_2,H_2SO_4$: C, 37·0; H, 4·8; N, 14·4%]. A second preparation gave 3·96 g. of cytidine sulphate.

Cytidine sulphate (2 g.) was converted by the method of Gulland and Smith (*J.*, 1948, 1527) into the free nucleoside (1·30 g.), m. p. 212—215° (undepressed on admixture with cytidine prepared from cytidylic acid), $[\alpha]_D^{25}$ +34·2° (*c*, 2·0 in water) (Found: C, 44·7; H, 5·3; N, 17·2. Calc. for $C_9H_{13}O_5N_3$: C, 44·4; H, 5·35; N, 17·3%).

Behaviour of Cytidine in Boiling 2% Sulphuric Acid.—Cytidine (0·3 g.) was heated under reflux in 2% w/v sulphuric acid (20 c.c.) for 2 hours. The solution was cooled and tested with Nessler's solution. A yellow colour was noticeable but no precipitate appeared, showing that deamination of cytidine had not occurred to any marked extent under these conditions.

Behaviour of Cytidylic Acid in Boiling 50% Aqueous Pyridine.—Cytidylic acid (1 g.) was heated under reflux in 50% aqueous pyridine (50 c.c.) for 100 hours (extent of hydrolysis, 82%). The solution was chromatographed on acid-washed Whatman No. 1 filter paper (Hanes and Isherwood, *Nature*, 1949, **164**, 1107), using *tert.*-butanol–pyridine–water (60 : 15 : 25). Uridine, cytidine, and uridylic and cytidylic acids were used as markers. The chromatogram was examined by photographing it in ultra-violet light on Ilford Reflex Document Paper No. 50 (Markham and Smith, *loc. cit.*; *Biochem. J.*, 1949, **45**, 294). Pronounced spots corresponding to uridine (R_F 0·67) and cytidine (R_F 0·51) and a fainter one corresponding to cytidylic acid (R_F 0·24) were observed.

Chromatographic Examination of the Aqueous Pyridine Hydrolysate of Yeast Ribonucleic Acid.—Yeast ribonucleic acid (1 g.) was heated under reflux in 50% aqueous pyridine (60 c.c.) for 103 hours (extent of hydrolysis, 57%). The solution was chromatographed as above. Guanosine (R_F 0·51), adenosine (R_F 0·59), cytidine (R_F 0·51), uridine (R_F 0·67), guanylic acid (R_F 0·26), yeast adenylic acid (two spots; R_F values, 0·24 and 0·30), cytidylic acid (R_F 0·24), and uridylic acid (R_F 0·36) were used as markers. The hydrolysate gave five spots with R_F values 0·24, 0·34, 0·52, 0·59, and 0·66.

The author thanks Professor A. R. Todd, F.R.S., for his interest and advice. Part of this investigation was conducted during the tenure of a Beit Memorial Fellowship for Medical Research.

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428. *The Relation between the Constitution of Arsenicals and their Action on Cell Division.*

By Harold King and R. J. Ludford.

Since cacodylic acid is a mitotic poison some homologues and other readily accessible types of aliphatic arsenical were synthesised and their action on living cells was examined by a tissue-culture technique. Two main types of mitotic aberrations were found, dependent on whether the action was primarily on the spindle ("colchicinic effect") or on the chromosomes.

It has become customary to apply the term mitotic poison to any substance capable of bringing about aberrations of mitosis in animal or plant cells. Mitotic poisoning of mammalian cells has acquired practical significance in the search for chemotherapeutic agents capable of inhibiting malignant growth.

Dustin and his collaborators first directed attention to the profound disturbance of cell division which followed the injection of arsenicals into mice (Piton, *Arch. Int. Med. Exp.*, **1929**, **5**, 355; Dustin and Piton, *Bull. Acad. Roy. Med. Belg.*, **1929**, **9**, 26; Dustin and Grégoire, *Compt. rend. Soc. Biol.*, **1933**, **114**, 195; *Bull. Acad. Roy. Med. Belg.*, **1933**, **13**, 585). Cacodylic acid was the most potent of the compounds investigated [(others were arsenious oxide, methylarsonic acid, and aminophenylarsonic acid (atoxyl)] and it also stimulated mitosis in cells of the crypts of Lieberkühn and of transplanted tumours. The chromosomes of dividing cells were described as being clumped together in the middle of each cell and being surrounded by clear œdematous-looking cytoplasm.

Interest in the arsenicals became diverted by the discovery of the unique mitotic poisoning properties of the alkaloid colchicine. By employing the tissue-culture technique, Ludford (*Arch. Exp. Zellforsch.*, **1936**, **18**, 411) showed that the cytological actions of colchicine and cacodylic acid were identical. Both substances arrested mitosis at metaphase by preventing the formation of the mitotic spindle.

Owing to the complexity of the colchicine molecule it seemed to us that, for investigating the relation between chemical constitution and mitotic poisoning, arsenicals would provide an ideal class of compound. In this investigation attention has been confined to the following: (i) methyl-, propyl-, butyl-, benzyl-, and 2-phenylethyl-arsonic acids, $R{\cdot}AsO_3H_2$; (ii) dimethyl-, diethyl-, and dibutyl-arsonous acids, $R_2AsO(OH)$; and (iii) 3-ethylamino-, 3-propylamino-, 3-butylamino-, 3-benzylamino-, 3-2′-phenylethylamino- and 3-*cyclo*hexylamino-propylarsonic acids, $R{\cdot}NH{\cdot}[CH_2]_3{\cdot}AsO_3H_2$.

Tissue cultures of mouse fibroblasts have been employed. The compounds were either applied to the cultures after active growth had commence or introduced into the media at the time of preparing the cultures, as neutral solutions in distilled water. Control cultures received the same amount of distilled water.

Most of the substances examined exhibited a mitotic poisoning over a relatively small range of concentrations. With each the aim has been to determine the concentration at which it interferes with the normal course of mitosis without appreciably damaging "resting cells."

The mitotic aberrations observed were of two main types, determined by whether the action was primarily on the mitotic spindle or on the chromosomes. The former results in the arrest of mitosis at metaphase, with the chromosomes either scattered throughout the cytoplasm or forming a cluster in the centre of the cell. This is the characteristic effect induced by colchicine. Of the substances listed below only dimethyl- and diethyl-arsonous acids and the thioarsinite formed from the former and cysteine have induced this mitotic aberration specifically. The action of the other arsenicals on the chromosomes is manifested by their distortion and fusion. Irregularities in the separation of the chromosomes to opposite poles of the mitotic spindle are extremely common. Chromosomes exhibit "stickiness," resulting in "bridges." Occasionally fragmentation is seen. Fusion of chromosomes may occur at metaphase or during anaphase. The most intense mitotic poisoning results in fusion of chromosomes at late prophase, thereby completely arresting mitosis.

The relative activities of the arsenicals examined were as given in the Table.

The following *N*-substituted derivatives of 3-aminopropylarsonic acid exhibited varying degrees of mitotic activity in dilutions between 1/10,000 and 1/25,000: *NN*-dimethyl, *N*-methyl, *N*-ethyl, *N*-butyl, *N*-hexyl, *N*-*cyclo*hexyl, *N*-benzyl, and *N*-2-phenylethyl. The last two were the best mitotic poisons in this group. One tervalent arsenical of this type was tested, namely, 3-(1-phenylethylamino)propylarsine dichloride, which was active at 1/100,000.

$Me_2AsO(OH)$	Cytological action similar to that of colchicine. Marked activity in dilutions of 1/50,000—1/75,000. Some activity at 1/100,000.
$Et_2AsO(OH)$	Not such a good mitotic poison as cacodylic acid. Active in concns. up to 1/100,000.
$Bu^n_2AsO(OH)$	Inactive within the range of dilutions used.
$Me_2As{\cdot}S{\cdot}CH_2{\cdot}CH(NH_2){\cdot}CO_2H$	Better mitotic poison at 1/100,000 than cacodylic acid.

The remaining compounds act primarily on the chromosomes. The mitotic aberrations are not of the "colchicinic" type.

$Ph_2AsO(OH)$	Active over a wide range of concns. 1/50,000–1/200,000.	
$(p\text{-}NH_2{\cdot}C_6H_4)_2{\cdot}AsO(OH)$	Inactive within the range of dilutions employed.	
$Me{\cdot}AsO(OH)_2$	Comparable activity at	1/5,000
$Pr^n{\cdot}AsO(OH)_2$	,, ,,	1/75,000
$CH_2{:}CH{\cdot}CH_2{\cdot}AsO(OH)_2$	,, ,,	1/75,000
$Bu^n{\cdot}AsO(OH)_2$	,, ,,	1/700,000
$C_6H_5{\cdot}AsO(OH)_2$	,, ,,	1/10,000
$C_6H_5{\cdot}CH_2{\cdot}AsO(OH)_2$	,, ,,	1/50,000
$C_6H_5{\cdot}CH_2{\cdot}CH_2{\cdot}AsO(OH)_2$	,, ,,	1/100,000
$NH_2{\cdot}[CH_2]_2{\cdot}AsO(OH)_2$	,, ,,	1/10,000—1/25,000

Preparation of some of the arsenicals used in this investigation is described in the Experimental section. We are indebted to Professor F. Challenger of Leeds University for a gift of propylarsonic and diethylarsinic acids.

Experimental.

3-n-*Butylaminopropylarsonic Acid Hydrochloride.*—3-Chloropropylarsonic acid (6·07 g.), n-butylamine (17·6 c.c.), and alcohol (40 c.c.) were boiled under reflux for 12 hours. Alcohol and free butylamine were then removed by distillation, and complete removal of butylamine effected by addition of N-sodium hydroxide (10 c.c.) and distillation to dryness under reduced pressure. 3N-Hydrochloric acid (10 c.c.) was added and the solution again evaporated to dryness and finally extracted with absolute alcohol to remove sodium chloride. The alcoholic solution on concentration deposited glistening leaflets of 3-n-*butylaminopropylarsonic acid hydrochloride* (3·7 g.), which on recrystallization from boiling alcohol (20 c.c.) had m. p. 232° (Found: C, 30·8; H, 7·1; N, 4·8. $C_7H_{18}O_3NAs,HCl$ requires C, 30·5; H, 7·0; N, 5·1%).

3-n-*Propylaminopropylarsonic Acid Hydrochloride* (cf. Gough and King, *J.*, 1928, 2426).—n-Propylamine (11·0 g.) and 3-chloropropylarsonic acid (5·7 g.) were heated without extra solvent on the water-bath for 15 hours. The free propylamine was distilled off and the residue treated as above. 3-n-Propylaminopropylarsonic acid hydrochloride separated as microscopic plates which on crystallization from the minimum volume (5·5 parts) of boiling absolute alcohol gave the pure salt (2·66 g.), m. p. 210° in agreement with previously recorded data.

3-*Ethylaminopropylarsonic Acid Hydrochloride.*—3-Chloropropylarsonic acid (6·07 g.) and alcoholic ethylamine solution (24·3 g. of 33%) were heated in a sealed tube for 16 hours at 100°. Excess of ethylamine was removed by distillation under reduced pressure in the presence of strong aqueous sodium hydroxide, and the required *hydrochloride* was isolated from the neutralized solution by extraction with absolute alcohol and addition of acetone (yield, 3·0 g.). It crystallized from absolute alcohol in silky leaflets which, air-dried, melted indefinitely between 100° and 120° (Found: loss at 100°, 2·6. $C_5H_{14}O_3NAs,HCl,0{\cdot}5H_2O$ requires H_2O, 3·5%. Found, on anhydrous salt: C, 23·9; H, 6·2; Cl, 13·9. $C_5H_{14}O_3NAs,HCl$ requires C, 24·2; H, 6·1; Cl, 14·3%).

3-*Benzylaminopropylarsonic Acid Hydrochloride.*—3-Chloropropylarsonic acid (6·08 g.), benzylamine (19·5 c.c.), and absolute alcohol (20 c.c.) were boiled for 18 hours. When the reaction product was worked up as described above, *benzylaminopropylarsonic acid hydrochloride* (3·85 g.) separated from the alcoholic solution and on crystallization from the minimum volume (70 c.c.) of boiling absolute alcohol formed clusters of soft needles (3·45 g.), m. p. 240° (effervescence) (Found: C, 39·0; H, 5·8; N, 4·5. $C_{10}H_{16}O_3NAs,HCl$ requires C, 38·8; H, 5·5; N, 4·5%).

3-(2-*Phenylethylamino*)*propylarsonic Acid Hydrochloride.*—3-Chloropropylarsonic acid (5·66 g.) and 2-phenylethylamine (20·3 g.) were heated on a vigorously boiling water-bath for 15 hours. N-Sodium hydroxide (50 c.c.) was added and the solution extracted exhaustively with ether. The aqueous solution was then made just acid to Congo-red paper by N-hydrochloric acid and then evaporated to dryness. The residue was extracted with boiling absolute alcohol, and on concentration of the extract 3-(2-*phenylethylamino*)*propylarsonic acid hydrochloride* (7·0 g.) separated. It crystallized from the minimum volume (130 c.c.) of boiling absolute alcohol in leaflets, m. p. 247—248° with resolidification to the anhydride (Found: C, 40·8; H, 5·9; N, 4·5; As, 23·5. $C_{11}H_{18}O_3NAs,HCl$ requires C, 40·8; H, 5·9; N, 4·3; As, 23·2%).

3-cyclo*Hexylaminopropylarsonic Acid Hydrochloride.*—3-Chloropropylarsonic acid (6·07 g.) and *cyclo*hexylamine (20·7 c.c.) were heated on the vigorously boiling water-bath for 24 hours. Unchanged *cyclo*hexylamine having been removed by ether extraction from the solution made strongly alkaline, the aqueous solution was neutralized to Congo-red paper and evaporated to dryness. The required 3-cyclo*hexylaminopropylarsonic acid hydrochloride* (6·1 g.) was extracted with absolute alcohol. It required 3 volumes of absolute ethyl alcohol for recrystallization and separated in clusters of small pointed needles, m. p. 172—173° (Found: C, 36·3; H, 7·6; N, 4·7. $C_9H_{20}O_3NAs,HCl$ requires C, 35·8; H, 7·0; N, 4·6%).

2-Amino-2-carboxyethyl Dimethylthioarsinite.—Cysteine hydrochloride (4·73 g.) and cacodylic acid (1·35 g., 0·3 mol.) were each dissolved in water (10 c.c.) and the solutions mixed. Some heat was developed and after 5 minutes cystine began to separate. N-Sodium hydroxide solution (30 c.c.) was then added, with cooling. Finally the solution was saturated with carbon dioxide and kept for 12 hours. The cystine (2·4 g.) was collected. On concentration of the filtrate *in vacuo* over sulphuric acid, *2-amino-2-carboxyethyl dimethylthioarsinite* (*S-dimethylarsinocysteine*) (4·25 g.) separated. It crystallized from water (8 c.c.) in shining needles, m. p. 219—220° (decomp.) (Found: C, 26·0; H, 5·6; N, 6·7; S, 13·6. $C_5H_{11}O_2NSAs$ requires C, 26·6; H, 5·4; N, 6·2; S, 14·2%). This thioarsinite slowly dissolves in sodium hydrogen carbonate solution and then gives no nitroprusside reaction, but if dissolved in sodium hydroxide solution it gives a strong reaction.

Benzylarsonic Acid.—This acid was prepared by the method of Quick and Adams (*J. Amer. Chem. Soc.*, 1922, **44**, 811) who give m. p. 167—168°, but in our hands it always had m. p. 196—197° (Found: C, 39·4; H, 4·0. Calc. for $C_7H_9O_3As$: C, 38·9; H, 4·2). Dehn and McGrath (*J. Amer. Chem. Soc.*, 1906, **28**, 354) also give m. p. 167°.

2-Phenylethylarsonic Acid.—Phenylethyl bromide (18·5 g.) and arsenious oxide (9·9 g.), dissolved in 10N-sodium hydroxide solution (30 c.c.), were boiled with vigorous stirring for 28 hours. The solution was extracted with ether, to remove unchanged phenylethyl bromide, and neutralized to litmus, and the arsenious oxide removed. When the filtrate was made acid to Congo-red paper, *phenylethylarsonic acid* (3·0 g.) separated. It crystallized from boiling water (50 c.c.) in thin hexagonal plates, m. p. 153° (Found: C, 42·2; H, 4·8. $C_8H_{11}O_3As$ requires C, 41·7; H, 4·8%).

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429. *Experiments on the Interaction of Hydroxy-compounds and Phosphorus and Thionyl Halides in the Absence and in the Presence of Tertiary Bases. Part VIII.*

By W. Gerrard, A. Nechvatal, and Barbara M. Wilson.

tert.-Butylcarbinol (*neo*pentyl alcohol) interacts readily with thionyl and phosphorus chlorides, thereby forming the chloro-esters, RO·SOCl and RO·PCl_2. In an ethereal solution containing pyridine, thionyl chloride effects an almost quantitative precipitation of pyridine hydrochloride and the formation of the sulphite, $(RO)_2SO$. In a similar way, the phosphite, $(RO)_3PHO$, was isolated in the phosphorus trichloride system, and corresponding experiments with phosphorus tribromide and with the oxyhalides of phosphorus are described.

Halogen and the hydrogen phosphite afforded the halogenophosphates, $(RO)_2POCl$, $(RO)_2POBr$, and, although chlorine reacted with the sulphite, definite information as to the consequences have not yet been obtained.

Therefore, although these experiments provide further evidence of the reluctance which *tert.*-butylcarbinol shows towards replacement of the hydroxyl group by halogen, presumably because this involves a sterically hindered "end-on" approach to the alcoholic carbon atom, they demonstrate a ready response to four-centre "broadside" reactions concerning the oxygen–hydrogen bond.

A remarkable observation was made by Dostrovsky, Hughes, and Ingold (*J.*, 1946, 173) that *tert.*-butylcarbinyl bromide (*neo*pentyl bromide) showed little response to the S_N1 ethoxylation mechanism, in accordance with its constitution as a primary bromide but nevertheless demonstrating a rapid damping of the influence of the three methyl groups attached to the carbon atom adjacent to the reactive one. More remarkable, indeed, was the observation that the rate constant for the S_N2 mechanism was extremely small, the activation energy being abnormally large. This reluctance has been explained in terms of steric hindrance to end-on approach of the entering group, HO ⟶ C — · · · Br.

Whitmore and Rothrock (*J. Amer. Chem. Soc.*, 1932, **54**, 3431) had previously drawn attention to the resistance which *tert.*-butylcarbinol shows to replacement of its hydroxyl group by a halogen atom through the agency of, *e.g.*, thionyl chloride and phosphorus tribromide.

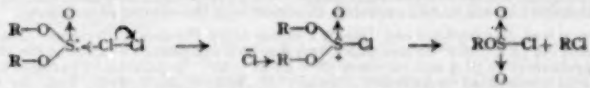
Therefore it appeared of interest to study what we term the "broadside" (four-centre) reactions of *tert.*-butylcarbinol with inorganic halides, such reactions being concerned with the link between the oxygen and the hydrogen atom of the hydroxyl group.

By the addition of the alcohol to thionyl chloride, *tert.*-butylcarbinyl chlorosulphinate, RO·SOCl, was readily formed. Addition of either this product (1 mol.) or thionyl chloride (0·5 mol.) to an ethereal solution of the alcohol (1 mol.) and pyridine (1 mol.) gave rise immediately to di-*tert.*-butylcarbinyl sulphite, $(RO)_2SO$, and pyridine hydrochloride. Further-

more, interaction between the sulphite and thionyl chloride occurred, and the chlorosulphinate was formed. These reactions are depicted as " broadside " reactions, and for this type *tert.*-butylcarbinol behaves as does, *e.g.*, butan-1-ol (Gerrard, *J.*, 1939, 99; 1940, 218):

Gerrard suggested that pyridine facilitates this process by formation of the hydrogen bond, $ROH{\cdot}{\cdot}{\cdot}NC_5H_5$, and Cleverdon and Smith (*Chem. and Ind.*, 1948, 29) have obtained dipole-moment evidence of the formation of this bond.

The behaviour of the chlorosulphinate on being heated with a small amount of pyridine hydrochloride was very different from that of a number of chlorosulphinates examined by French and Gerrard (*J.*, 1949, 3326). Instead of a clean and smooth conversion into the chloride, RCl, and sulphur dioxide at a relatively low temperature (60—70°), the chlorosulphinate showed a reluctance to decompose even at 110°. The products obtained were thionyl chloride, the sulphite $(RO)_2SO$, and what was most likely a mixture of *tert.*-amyl chloride and *tert.*-butylcarbinyl chloride. Although the sulphite readily absorbed a molecular proportion of chlorine (cf. Cross and Gerrard, *J.*, 1949, 2686) there was no definite evidence available to indicate that the reaction had proceeded by the sequence:



Tri-*tert.*-butylcarbinyl phosphite was the main distilled product of the interaction of the alcohol (1 mol.) and the trihalide (0·33 mol.) in the presence of pyridine (1 mol.), although it was contaminated by a little of the hydrogen phosphite. The precipitation of the pyridine hydrohalide was rapid in ethereal solution, and the behaviour of the system was similar to that of the butan-1-ol system (Gerrard, *J.*, 1940, 464).

There is evidence (Gerrard, *loc. cit.*; *J.*, 1944, 85; 1945, 848) for believing that in the examples of such alcohols as butan-1-ol and octan-2-ol, the chloride RCl is formed by the rapid interaction of hydrogen chloride and the tri-ester which are formed during the primary reactions occurring between the alcohol (1 mol.) and the trichloride (0·33 mol.). This rapid attack very probably follows the course: $(RO)_3P: + HCl \longrightarrow Cl^- + (RO)_3\overset{+}{P}{:}H \longrightarrow ClR + (RO)_3PHO$. Subsequent dealkylation of the phosphite is slow at room temperature, presumably because the " lone-pair " mechanism is no longer available. It is interesting to find that, in the example of *tert.*-butylcarbinol, the interaction with phosphorus trichloride or tribromide (0·33 mol.) leads to the isolation of the phosphite as the main product, no halide RX being found.

When the alcohol was added to excess of trichloride, *tert.*-butylcarbinyl dichlorophosphinite, $RO{\cdot}PCl_2$, was isolated in 80% yield.

The phosphate, $(RO)_3PO$, was obtained by means of phosphorus oxychloride or oxybromide, in the presence of pyridine.

Interaction of chlorine and the tri-*n*-butyl phosphite was studied by Gerrard (*loc. cit.*), and McCombie, Saunders, and Stacey (*J.*, 1945, 380) have shown that halogens readily react with hydrogen phosphites to give the halogenophosphate $(RO)_2POX$ and hydrogen halide (cf. Gerrard and Philip, *Research*, 1948, **1**, 477). End-on approach to the carbon atom is not involved, and we readily obtained di-*tert.*-butylcarbinyl dichloro- and dibromo-phosphonate. These afforded the phosphate, $(RO)_3PO$, by interaction with alcohol and pyridine.

As Dostrovsky, Hughes, and Ingold (*Nature*, 1947, **160**, 901) felt that Gerrard and Nechvatal (*ibid.*, 1947, **159**, 812) had not given the right emphasis in their interpretation of statements by Whitmore and Rothrock (*loc. cit.*), we deem it desirable to elucidate this matter now for future reference.

Whitmore and Rothrock described, in some detail, evidence of interaction with sulphuric acid involving the replacement of the hydrogen atom of the hydroxyl group. Their evidence

concerning thionyl chloride was presented in such a way as to compel a reader to infer that neither the hydroxyl group as a whole, nor the hydrogen atom of the hydroxyl group had undergone reaction : the authors specifically declared that the alcohol (80%) had been recovered. According to our experiments, those authors had the sulphite $(RO)_2SO$ (0·5 mol., from 1 mol. each of alcohol and pyridine) and thionyl chloride (about 0·5 mol.) in the ethereal solution after the initial mixing. Either the temperature of the reaction mixture was sufficiently high, during the period of storage, to convert a considerable amount of the sulphite into the chlorosulphinate, which water would hydrolyse to the alcohol, or the treatment with water (presumably given) was so unusually vigorous as to hydrolyse a considerable amount of the sulphite itself. In their phosphorus tribromide experiment, they obtained a yield of 14% of the bromide RBr; but apart from this, they claim recovery of the alcohol.

Therefore their statement " the inactivity of *neo*pentyl alcohol to heat and reagents has been demonstrated " applied precisely to their experiment with thionyl chloride (as their evidence was presented) with respect both to the hydroxyl group as a whole and to the hydrogen atom of the hydroxyl group considered separately. To their experiment with phosphorus tribromide their statement applied qualitatively (inactivity replaced by low activity) to the replacement of the hydroxyl group, since a yield of 14% of the bromide was isolated, but again applied precisely to the replacement of hydrogen separately.

Experimental.

Notes on Procedure.—Dry ether, kept over sodium, was used throughout. Precipitates obtained when pyridine was used in an experiment were separated by filtration and kept in a vacuum for 1—2 hours before being weighed and analysed, without further treatment. Unless otherwise stated, "aqueous treatment " refers to washing first with water, then with a dilute solution of sodium carbonate, followed by drying (K_2CO_3) and storage over sodium sulphate. When pyridine had been used, washing with a dilute solution of sulphuric acid was carried out before treatment with the solution of carbonate.

Interaction of tert.*-Butylcarbinol and Thionyl Chloride in the Presence of Pyridine.*—Thionyl chloride (2·97 g., 0·5 mol.) in 15 c.c. of ether was added dropwise to a well-shaken solution of the alcohol (4·4 g., 1 mol.) and pyridine (3·95 g., 1 mol.) in ether (20 c.c.) at −15°. Separation of pyridine hydrochloride (5·31 g., 92·1%) commenced immediately (Found : Cl, 30·2; C_5H_5N, 68·0. Calc. for C_5H_5N,HCl : Cl, 30·8; C_5H_5N, 68·4%), and from the washed ethereal solution *di*-tert.*-butylcarbinyl sulphite* (85%), b. p. 103°/12 mm., n_D^{15} 1·4263 (Found : SO_3, 28·6. $C_{10}H_{22}O_3S$ requires SO_3, 28·8%), was obtained.

When 1·2 mols. of thionyl chloride were used instead of 0·5 mol. and the primary reaction mixture was set aside for 12 hours in order to follow Whitmore and Rothrock's procedure in that detail, the products isolated were *tert.*-butylcarbinol (0·3 g.), b. p. 30°/15 mm., and the sulphite (3·5 g.), b. p. 105—106°/15 mm. (from 5·0 g. of alcohol).

Interaction of Di-tert.*-butylcarbinyl Sulphite and Thionyl Chloride.*—Thionyl chloride (1·63 g., 1·1 mols.) was added dropwise to the sulphite (2·77 g., 1 mol.) at −15° and agitated by a stream of dry nitrogen, and the resulting mixture was then kept for 1 hour at 17° and for 30 minutes at 70—80°. On distillation without aqueous treatment, tert.*-butylcarbinyl chlorosulphinate* (2·78 g.), b. p. 64—67°/12 mm. (Found : Cl, 19·4. $C_5H_{11}O_2ClS$ requires Cl, 20·8%, see later), and di-*tert.*-butylcarbinyl sulphite (0·725 g.), b. p. 102°/12 mm. (Found : SO_3, 28·6%), were obtained. The chlorosulphinate fumed in moist air and reacted vigorously with water.

Interaction of tert.*-Butylcarbinol and Thionyl Chloride.*—The alcohol (4·4 g., 1 mol.) in ether (15 c.c.) was added dropwise to thionyl chloride (9·31 g.) at −15°. After the mixture had been gradually (1 hour) warmed to 70°, it was distilled, whereupon *tert.*-butylcarbinyl chlorosulphinate (6·9 g.), b. p. 58·5°/11 mm., n_D^{15} 1·4515 (Found : Cl, 20·7; SO_3, 36·1. Calc. for $C_5H_{11}O_2ClS$: Cl, 20·8; SO_3, 37·6%, see previous experiment), and di-*tert.*-butylcarbinyl sulphite (0·55 g.), b. p. 102°/12 mm., n_D^{15} 1·4268, were obtained.

Interaction of tert.*-Butylcarbinol and* tert.*-Butylcarbinyl Chlorosulphinate in the Presence of Pyridine.*—The chlorosulphinate (2·55 g., 1 mol.) was added dropwise to a shaken mixture of alcohol (1·32 g., 1 mol.) and pyridine (1·19 g., 1 mol.) in ether (15 c.c.) at −15°. Pyridine hydrochloride (1·50 g.) (Found : Cl, 30·05; C_5H_5N, 68·3%) began to form immediately, and after 1 hour at 15° filtration and aqueous treatment of the ethereal solution led to isolation of di-*tert.*-butylcarbinyl sulphite (3·0 g., 91%), b. p. 99—100°/10 mm., $n_D^{15\cdot5}$ 1·4268 (Found : SO_3, 28·6%).

Decomposition of the Chlorosulphinate.—The chlorosulphinate (5·35 g.) was heated at 70° for one hour with 0·03 g. (0·01 mol., approx.) of pyridine hydrochloride. On distillation of the reaction mixture, the chlorosulphinate (4·78 g.) was recovered. The temperature of the recovered material (again in presence of pyridine hydrochloride, 0·03 g.) was raised from 70° to 110° during 1 hour. A colourless liquid (0·25 g.) distilled. Distillation of the reaction mixture at 12 mm. then resulted in the recovery of 3·0 g. of the chlorosulphinate, the sulphite R_2SO_3 (0·3 g.) also being obtained.

The chlorosulphinate (6·0 g.) and hydrochloride (0·04 g.) were heated for 2 hours at 110°, and then the temperature was raised to 150° during 1 hour. The colourless distillate (3·25 g.), b. p. 76—81°, fumed in air, and from behaviour on re-distillation and analysis appeared to be a mixture of thionyl chloride (1·41 g.), *tert.*-amyl chloride, and *tert.*-butylcarbinyl chloride (total chloride, RCl, 1·66 g.). The chloride (RCl) distillate was dissolved in ether and given aqueous treatment. A distillate (1·5 g.), b. p. 83—84° (Found : C, 56·6; H, 10·4; Cl, 31·7. Calc. for $C_5H_{11}Cl$: C, 56·3; H, 10·3; Cl, 33·3%), was obtained.

From hydrolytic behaviour of this material in the presence of water we believe it to be a mixture of the two chlorides just referred to, these having very nearly the same b. p.

The residue (1·0 g.) from the primary heat treatment had b. p. 100—101°/15 mm. (Found: SO_3, 27·6%) and was identified as the sulphite $(RO)_2SO$.

When pyridine hydrochloride was omitted for the heat treatment, there was no distillate whilst the chlorosulphinate was kept at 110° for 2 hours. On the temperature being slowly raised (4 hours) to 160° a distillate (1·3 g.), b. p. 74°, of a similar character to that of the previous experiment, was obtained. 0·5 G. of chlorosulphinate was recovered, and 0·7 g. of sulphite was obtained.

*Interaction of Chlorine and Di-*tert.*-butylcarbinyl Sulphite.*—After chlorine had been passed through the sulphite (6·6 g.) for 1 hour at −10°, the liquid became yellow, indicating excess of (unchanged) chlorine. When attempts were made to isolate a chloride RCl, the material decomposed (oil-bath, 110°), hydrogen chloride and sulphur dioxide being evolved. Continuing the process under reduced pressure we obtained the sulphite (1·0 g.) and a thick tar (4·5 g.). Treatment with water and a solution of sodium carbonate, followed by drying before distillation, led to no improvement.

Interaction of tert.*-Butylcarbinol and the Halides and Oxyhalides of Phosphorus in the Presence of Pyridine.*—(1) *Trichloride.* Phosphorus trichloride (2·29 g., 0·33 mol.) in ether (15 c.c.) was added to a well-shaken mixture of the alcohol (4·4 g., 1 mol.) and pyridine (3·95 g., 1 mol.) in ether (15 c.c.) at −15°. Pyridine hydrochloride (5·29 g., 92%) (Found: Cl, 30·4; C_5H_5N, 68·5%) was formed immediately, and evaporation of the ethereal solution, after aqueous treatment, left a residue (4·4 g. Calc. for the tri-ester, 4·8 g.) (Found: P, 10·0; no chlorine. The *tri-ester* $C_{15}H_{33}O_3P$ requires P, 10·6%). From this was obtained *di-*tert.*-butylcarbinyl hydrogen phosphite* (3·84 g.), b. p. 116—119°/13 mm., n_D^{15} 1·4200 (Found: P, 14·0. $C_{10}H_{23}O_3P$ requires P, 13·95%). When the filtrate from the reaction mixture was distilled without treatment with water, a white solid, b. p. 71°/1 mm. (Found: P, 11·3%), accounted for nearly all the alcohol used. From its behaviour with hydrogen halides, we conclude that this product was the tri-ester mixed with a little hydrogen phosphite.

(2) *Tribromide.* Pyridine hydrobromide (7·86 g., 98·3%) (Found: Br, 48·9; C_5H_5N, 48·0. Calc. for C_5H_5N,HBr: Br, 50·0; C_5H_5N, 49·4%) and, from the washed ethereal solution, a residue (4·12 g.) (Found: P, 10·3; Br, 0%) were obtained. Distillation afforded *di-tert.*-butylcarbinyl hydrogen phosphite (3·6 g.), b. p. 115—117°/12 mm. (Found: P, 14·0%). The weight of alcohol used was the same as in the previous experiment.

(3) *Oxychloride.* Phosphorus oxychloride (2·56 g., 0·33 mol.) in ether (15 c.c.) was added to the alcohol (4·4 g., 1 mol.) and pyridine (3·95 g., 1 mol.) in ether (20 c.c.) at −15°. Although precipitation of the hydrochloride commenced immediately, it was incomplete even after 16 hours at 15°. The precipitate (3·95 g., 68·5%) (Found: Cl, 30·7; C_5H_5N, 68·6%) was separated, and from the washed ethereal solution a residue (4·35 g.) (Found: P, 12·0; Cl, 0%) was obtained which afforded a white sublimate (0·3 g.), b. p. 30—40°/20 mm., a waxy solid (*tri-*tert.*-butylcarbinyl phosphate*) (2·3 g.), b. p. 149—152°/14 mm., m. p. 80° (Found: P, 10·9. $C_{15}H_{33}O_4P$ requires P, 10·05%), and a brown residue.

(4) *Oxybromide.* Phosphorus oxybromide, prepared as described by Gerrard, Nechvatal, and Wyvill (*Chem. and Ind.*, 1947, 437) (4·90 g., 0·33 mol.), in ether (20 c.c.) was added to the alcohol (4·52 g., 1 mol.) and pyridine (4·06 g., 1 mol.) in ether (20 c.c.) at −15°. Precipitation of pyridine hydrobromide (7·65 g., 93·4%) (Found: Br, 49·9; C_5H_5N, 49·5%) commenced immediately and proceeded much more rapidly than with the oxychloride. The mixture was filtered after 2 days, and on evaporation of the washed ethereal solution there was left a white solid (4·7 g.) (Calc. for the tri-ester, 5·1 g.) (Found: P, 10·1; Br, 0%), which on distillation afforded a white waxy solid, b. p. 152°/11 mm., m. p. 84—85° (Found: P, 10·0%), and a residue, 0·2 g.

Interaction of Phosphorus Trichloride and tert.*-Butylcarbinol.*—(1) The trichloride (2·29 g., 0·33 mol.) was added dropwise to the alcohol (4·4 g., 1 mol.) at −15°, nitrogen being passed through the reaction vessel and thence to absorption tubes containing pellets of potassium hydroxide. Hydrogen chloride (0·034 g.) was evolved during mixing, a further 0·96 g. whilst the mixture warmed to 15°, and a further 0·165 g. whilst it was warmed to 50—60° for 15 minutes, the total weight being equivalent to 0·66 mol. The product then yielded a sublimate of *tert.*-butylcarbinol (0·37 g.), b. p. 30—35°/10 mm., m. p. 45°, and the hydrogen phosphite $(RO)_2P{\cdot}OH$ (3·32 g.), b. p. 109°/10 mm., n_D^{15} 1·4200 (Found: P, 13·9%).

(2) The alcohol (1·76 g., 1 mol.) in ether (10 c.c.) was added to the trichloride (4·4 g.) at −15°, whilst nitrogen was passed through the reaction liquid. Hydrogen chloride (1 mol.) was evolved when the reaction mixture was set aside for 3 hours at 15°, and for 30 minutes whilst it was warmed to 70°. Trichloride carried over was allowed for in this estimation. tert.*-Butylcarbinyl dichlorophosphinite* was obtained as a colourless fuming liquid (3·03 g., 80%), b. p. 47·5—49°/10 mm., without residue (Found: Cl, 37·6; P, 16·4. $C_5H_{11}OCl_2P$ requires: Cl, 37·6; P, 16·4%).

Interaction of Phosphorus Tribromide and tert.*-Butylcarbinol.*—(1) The tribromide (4·52 g., 0·33 mol.) was added dropwise to the alcohol (4·4 g., 1 mol.) at −15°, a stream of nitrogen being passed through as in the experiment with the trichloride. After the reaction mixture had been kept at 15° for 1·5 hours and gradually warmed (30 minutes) to 80°, the alcohol (0·5 g.), b. p. 30—35°/9 mm., m. p. 43°, the hydrogen phosphite (2·06 g.), b. p. 106—108°/9 mm., n_D^{15} 1·4240 (Found: P, 14·4%), and a residue of tar (0·64 g.) were obtained. In a second experiment the primary mixture, obtained by addition of the tribromide (4·5 g., 0·33 mol.) dropwise to the alcohol (4·4 g., 1 mol.) without solvent at −10°, was set aside for 12 hours at 15°. It was then mixed with ice (wash-water contained 0·0064 g. of P), and the dried ethereal extract was evaporated at low pressure, the temperature being slowly raised to 100°. A liquid (0·3 g.) which appeared to be a mixture of the two halides, RBr, was collected. The residue (3·04 g.) (Found: P, 12·6%) had b. p. 120°/20 mm. and distilled completely.

Interaction of Halogens and Hydrogen Halides and the Phosphorous Ester.—Passage of hydrogen chloride

into the solid tri-ester, obtained as described, resulted in the rapid formation of the hydrogen phosphite, but it was not clear whether chloride RCl was formed.

Passage of hydrogen bromide and of hydrogen iodide through the "phosphite" product (4·4 g.) obtained by distillation after water treatment led to *tert.*-amyl bromide (0·3 g.), b. p. 110—115° (decomp.), and *tert.*-amyl iodide (0·1 g.), b. p. 122°, but the bulk of the original material was recovered as hydrogen phosphite. When hydrogen bromide was passed through the recovered hydrogen phosphite at 15°, no *tert.*-amyl bromide was isolated, the bulk of the hydrogen phosphite being recovered.

Chlorine was passed into the hydrogen phosphite (4·04 g.) at room temperature for 15 minutes, after which the liquid became yellow. During this period, the liquid became warm, and hydrogen chloride was copiously evolved. From the residue, *di-tert.-butylcarbinyl chlorophosphonate*, $(RO)_2POCl$ (3·9 g.), b. p. 115—120°/12 mm., 90°/2 mm., m. p. 42·5°, was obtained as a white solid (Found: Cl, 13·4. $C_{18}H_{38}O_3ClP$ requires Cl, 13·8%).

This ester (2·5 g., 1 mol.) in ether (10 c.c.) was added to ethyl alcohol (0·8 g.) and pyridine (1·5 g.) in ether (10 c.c.) at −10°. Precipitation of pyridine hydrochloride commenced during the dropwise mixing and appeared to be well advanced after a few minutes. The mixture was set aside for 2 days, however, before filtration. Pyridine hydrochloride (0·78 g.) (Found: Cl, 30·3; C_5H_5N, 67·5%) was separated, and from the filtrate a liquid (1·8 g.), b. p. 83·5°/1 mm., and a residue (0·3 g.) were obtained. When *tert.*-butylcarbinol was used instead of ethyl alcohol, the rate of precipitation of pyridine hydrochloride was much slower, and was incomplete after 2 days. Unchanged alcohol (0·4 g.), b. p. 38°/12 mm., unchanged chlorophosphonate (0·46 g.), b. p. 115—116°/12 mm., and the tri-ester, $(RO)_3PO$ (0·94 g.), m. p. 84° (Found: P, 9·6%), were obtained.

Bromine vapour (3·6 g., 1·2 mols.) was passed into the hydrogen phosphite (4·4 g.) at room temperature. The mixture became warm and was cooled, and hydrogen bromide was copiously evolved. Distillation afforded *di-tert.-butylcarbinyl bromophosphonate* as a white solid (2·0 g.), b. p. 90°/1 mm. (Found: Br, 25·4. $C_{18}H_{38}O_3BrP$ requires Br, 26·6%), and a second white solid (1·0 g.), b. p. 160°/1 mm. (Found: Br, 3·0; P, 15·3%). Addition of the bromophosphonate (1·58 g.) to an ethereal solution of pyridine and ethanol caused pyridine hydrobromide (0·73 g.) to be precipitated much more readily than the hydrochloride was precipitated by the chlorophosphonate.

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430. *The Nitration of 4-Hydroxy- and 4-Chloro-3-methylquinoline.*

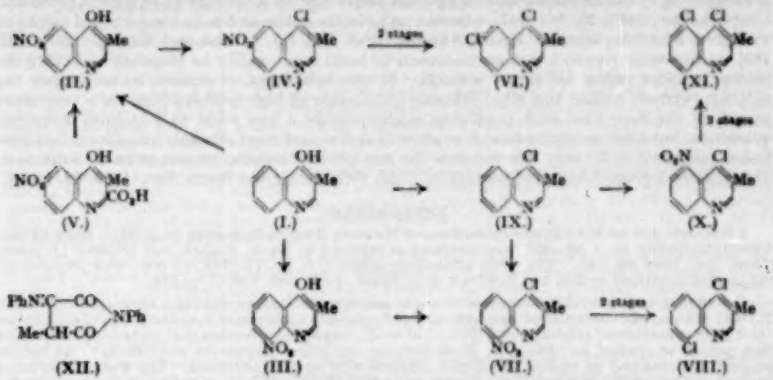
By A. ADAMS and D. H. HEY.

The nitration of 4-hydroxy-3-methylquinoline gives mainly 6-nitro-4-hydroxy-3-methylquinoline and a smaller proportion of 8-nitro-4-hydroxy-3-methylquinoline. From the product of the nitration of 4-chloro-3-methylquinoline, 4-chloro-5-nitro-3-methylquinoline and 4-chloro-8-nitro-3-methylquinoline are isolated. The identity of these nitration products is proved by their conversion into dichloro-3-methylquinoline of known constitution.

THE synthesis of some arylamino(dialkylaminoalkylamino)-quinaldines and -lepidines has recently been described (Adams and Hey, *J.*, 1949, 3185). In view of the antimalarial properties claimed for Sontochin [7-chloro-4-(1′-methyl-4′-diethylaminobutylamino)-3-methylquinoline] it was considered that attention should be directed to arylamino(dialkylaminoalkylamino)-derivatives of 3-methylquinoline. The present communication describes the preparation of some of the intermediate 4-chloro-*Bz*-nitro-3-methylquinolines required for the synthesis of 4-arylamino(dialkylaminoalkylamino)-3-methylquinolines. Although many substituted 4-chloro-3-methylquinolines have been described (Steck, Hallock, and Holland, *J. Amer. Chem. Soc.*, 1946, **68**, 129, 132, 380, and 1241; Breslow, Bloom, Shivers, Adams, Weiss, Yost, and Hauser, *ibid.*, p. 1232; Steck, Hallock, Holland, and Fletcher, *ibid.*, 1948, **70**, 1012; Steck and Hallock, *ibid.*, 1949, **71**, 890) there appears to be no record of the preparation of any 4-chloro-nitro-3-methylquinolines. Since previous experience in the quinaldine and lepidine series had shown that direct syntheses from nitroanilines were unlikely to be promising, attention was directed to the nitration of 4-chloro- and 4-hydroxy-3-methylquinoline, which compounds were readily accessible from ethyl ethoxalylpropionate and aniline by the method described by Steck, Hallock, and Holland (*ibid.*, 1946, **68**, 129).

Nitration of 4-hydroxy-3-methylquinoline (I), by using a mixture of concentrated nitric acid and sulphuric acid at 0—5°, proceeded smoothly and gave a mixture of nitro-4-hydroxy-3-methylquinolines in 83% yield, from which two pure isomerides were obtained. The greater portion (isolated as 76% of the mixture), m. p. >360°, which was almost insoluble in alcohol, proved to be 6-nitro-4-hydroxy-3-methylquinoline (II). The lesser portion (isolated as 21% of the mixture), m. p. 239—241°, which was readily soluble in alcohol, was 8-nitro-4-hydroxy-3-methylquinoline (III). The structure of (II) was proved by its conversion, on treatment with phosphorus oxychloride, into 4-chloro-6-nitro-3-methylquinoline (IV), identical with a specimen

prepared in small yield from ethyl ethoxalylpropionate and *p*-nitroaniline. When these compounds were boiled in benzene solution for 48 hours and the product ring-closed in boiling



phenyl ether, ethyl 6-nitro-4-hydroxy-3-methylquinoline-2-carboxylate was formed. Alkaline hydrolysis of this ester gave 6-nitro-4-hydroxy-3-methylquinoline-2-carboxylic acid (V) which, by being boiled with quinoline and copper bronze (cf. Kermack and Weatherhead, *J.*, 1940, 1168), was decarboxylated to give (II). Treatment of (II) with phosphorus oxychloride gave 4-chloro-6-nitro-3-methylquinoline (IV); further confirmation of the structures was obtained by reduction of (IV) to the amino-quinoline which, on diazotisation and treatment with cuprous chloride, gave 4 : 6-dichloro-3-methylquinoline (VI), the melting point of which was identical with that recorded by Breslow *et al.* (*loc. cit.*).

The structure of (III) was proved by its conversion on treatment with phosphorus oxychloride into 4-chloro-8-nitro-3-methylquinoline (VII), which was reduced to the 8-amino-compound and converted by a Sandmeyer reaction into 4 : 8-dichloro-3-methylquinoline (VIII), identical with an authentic specimen, prepared from *o*-chloroaniline and ethyl ethoxalylpropionate as described by Steck, Hallock, and Holland (*J. Amer. Chem. Soc.*, 1946, **68**, 132).

Similar nitration of 4-chloro-3-methylquinoline (IX) proceeded smoothly and gave a mixture of 4-chloro-nitro-3-methylquinolines in 70% yield. Separation of the isomerides proved to be difficult, probably owing to the formation of a eutectic mixture which could not be separated by crystallisation from alcohol, benzene, light petroleum (b. p. 60—80°), or N-hydrochloric acid, or by fractional precipitation from an acid solution by addition of alkali. Partial separation of the mixture was finally achieved by distillation with steam. After two recrystallisations from ethyl alcohol, the solid portion of the distillate gave 4-chloro-5-nitro-3-methylquinoline (X), whilst purification of the distillation residue gave the 8-nitro-compound (VII), identical with that previously described. The structure of (X) was proved by its reduction to 4-chloro-5-amino-3-methylquinoline and subsequent conversion by the Sandmeyer reaction into 4 : 5-dichloro-3-methylquinoline (XI), identical with an authentic specimen. The latter was prepared from ethyl ethoxalylpropionate and *m*-chloroaniline, as described by Steck, Hallock and Holland (*ibid.*, p. 380). No 4-chloro-6-nitro-3-methylquinoline was isolated from the nitration mixture.

Treatment of (II) with alkali and methyl sulphate gave 6-nitro-1 : 3-dimethyl-4-quinolone. On the other hand, when (IV) was boiled with a solution of sodium methoxide in methyl alcohol 6-nitro-4-methoxy-3-methylquinoline was obtained. By heating (IV) with *p*-chloroaniline, 6-nitro-4-*p*-chloroanilino-3-methylquinoline was formed, which was reduced with stannous chloride and concentrated hydrochloric acid to 6-amino-4-*p*-chloroanilino-3-methylquinoline.

The formation of ethyl 6-nitro-4-hydroxy-3-methylquinoline-2-carboxylate in low (22%) yield from ethyl ethoxalylpropionate and *p*-nitroaniline has been reported above; the overall yield of 6-nitro-4-hydroxy-3-methylquinoline was only 5%. The reaction between ethyl ethoxalylpropionate and *m*-nitroaniline gave a mixture of esters in 11% yield from which was isolated ethyl 5(or 7)-nitro-4-hydroxy-3-methylquinoline-2-carboxylate. No quinolinecarboxylic ester could be isolated from the product from ethyl ethoxalylpropionate and *o*-nitroaniline.

It is well-known that the reaction between aniline and ethyl acetoacetate gives either ethyl β-anilinocrotonate or acetoacetanilide according to whether low- or high-temperature conditions are employed. The crotonate may be cyclised above 250° to 4-hydroxyquinaldine (Conrad and Limpach, *Ber.*, 1887, **20**, 944, 947), whereas ring-closure of the anilide in concentrated sulphuric acid gives 2-hydroxylepidine (Knorr, *Annalen*, 1886, **236**, 75). Ewins and King (*J.*, 1913, **103**, 105) subsequently reported that acetoacetanilide could more readily be prepared by boiling the reactants under reflux for ninety seconds. It was considered of interest to investigate the reaction between aniline and ethyl ethoxalylpropionate at high temperatures for a very short period, in the hope that such conditions might provide a new route to 2-hydroxy-3-methylquinolines, but after an equimolecular mixture of aniline and ethyl ethoxalylpropionate had been boiled under reflux for only two minutes, the sole product isolated proved to be 2 : 5-diketo-4-phenylimino-1-phenyl-3-methylpyrrolidine (XII) (Wislicenus and Spiro, *Ber.*, 1889, **22**, 3351).

Experimental.

4-Hydroxy- and 4-Chloro-3-methylquinoline.—4-Hydroxy-3-methylquinoline, m. p. 231°, and 4-chloro-3-methylquinoline, m. p. 59—60°, were prepared as reported by Steck, Hallock, and Holland (*J. Amer. Chem. Soc.*, 1946, **68**, 131). The ethyl ethoxalylpropionate, b. p. 117—118°/11 mm., was prepared by the method described by Cox and McElvain (*Org. Synth.*, 1943, Coll. Vol. II, p. 272).

Nitration of 4-Hydroxy-3-methylquinoline.—The solution obtained by stirring a mixture of nitric acid (*d* 1·42; 4·9 c.c.) and concentrated sulphuric acid (5·0 c.c.) into a solution of 4-hydroxy-3-methylquinoline (10·6 g.) in concentrated sulphuric acid (50 c.c.) at 0—5°, was kept for two hours at room temperature and then poured on crushed ice (2000 g.). Next morning, the yellow precipitate was collected; no further product was obtained on making the filtrate alkaline with aqueous ammonia. The washed and dried product (11·3 g., 83%) was boiled vigorously with ethyl alcohol (500 c.c.) for fifteen minutes, and the mixture cooled and filtered. Recrystallisation of a small portion of the residue (8·5 g., 76% of the mixture) from a large quantity of alcohol gave *6-nitro-4-hydroxy-3-methylquinoline*, in pale yellow needles, m. p. >360° (Found: C, 58·5; H, 4·1. $C_{10}H_8O_3N_2$ requires C, 58·8; H, 3·9%). Evaporation to dryness of the original alcoholic filtrate gave *8-nitro-4-hydroxy-3-methylquinoline* (2·4 g., 21% of the mixture), which crystallised from alcohol in yellow needles, m. p. 239—241° (Found: C, 59·1; H, 3·9. $C_{10}H_8O_3N_2$ requires C, 58·8; H, 3·9%).

6-Nitro-1 : 3-dimethyl-4-quinolone.—A mixture of 6-nitro-4-hydroxy-3-methylquinoline (1·0 g.), potassium hydroxide (0·4 g.), water (10 c.c.), and methyl sulphate (0·7 g.) was shaken for 30 minutes. Next morning the precipitate was collected, washed with water, dried, and recrystallised from alcohol; *6-nitro-1 : 3-dimethyl-4-quinolone* (0·6 g.) separated in pale-yellow needles, m. p. 263—265° (Found: C, 60·7; H, 4·6. $C_{11}H_{10}O_3N_2$ requires C, 60·5; H, 4·6%).

4-Chloro-6-nitro-3-methylquinoline.—6-Nitro-4-hydroxy-3-methylquinoline (9·5 g.) was boiled under reflux with phosphorus oxychloride (50 c.c.) for two hours. The cooled solution was poured on crushed ice (1000 g.), and made alkaline with aqueous sodium hydroxide. The white precipitate was collected, washed with water, and dried. Recrystallisation from alcohol gave *4-chloro-6-nitro-3-methylquinoline* (6·0 g.) in colourless needles, m.p. and mixed m. p. 171·5° (with an authentic specimen prepared from *p*-nitroaniline as described below) (Found: C, 53·7; H, 3·2. $C_{10}H_7O_2N_2Cl$ requires C, 53·9; H, 3·2%).

6-Nitro-4-methoxy-3-methylquinoline.—4-Chloro-6-nitro-3-methylquinoline (1·0 g.) was boiled under reflux for three hours with a solution of sodium (0·11 g.) in methyl alcohol (40 c.c.). The cooled solution was stirred into water (400 c.c.), and the needles which separated were filtered off, washed with water, dried, and crystallised from light petroleum (b. p. 60—80°). *6-Nitro-4-methoxy-3-methylquinoline* (0·7 g.) separated in colourless rhombohedra, m. p. 146—147° (Found: C, 60·0; H, 4·6. $C_{11}H_{10}O_3N_2$ requires C, 60·5; H, 4·6%).

4-Chloro-8-nitro-3-methylquinoline.—*4-Chloro-8-nitro-3-methylquinoline*, prepared (in 92% yield) in the same way as the 4-chloro-6-nitro-compound (see above) and crystallised from alcohol in colourless needles, m. p. 125° (Found: C, 53·6; H, 3·6. $C_{10}H_7O_2N_2Cl$ requires C, 53·9; H, 3·2%).

Nitration of 4-Chloro-3-methylquinoline.—4-Chloro-3-methylquinoline (8·75 g.) was dissolved slowly, with mechanical stirring, in a mixture of fuming nitric acid (*d* 1·5; 30 c.c.), concentrated sulphuric acid (30 c.c.) at 0—5°. The solution was heated on the water-bath for five minutes and, after two hours at room temperature, was poured into ice-water (1 l.). No precipitate was formed. The following methods were used in attempts to isolate the products.

(*a*) The solution was made alkaline with aqueous sodium hydroxide, and the precipitated solid was collected, washed with water, and dried (7·75 g., 70%; m. p. 94—97°). Crystallisation from alcohol gave needles, m. p. 100—103°; recrystallisation from the same solvent did not raise the melting point of the bulk of the material, but a few crystals, m. p. 125° and m. p. 141·5°, were obtained from mother-liquors. The melting point of the main fraction was not raised by recrystallisation from light petroleum (b. p. 60—80°), methyl alcohol, benzene, or N-hydrochloric acid

(*b*) The aqueous solution was titrated with 8N-sodium hydroxide, and the precipitates collected after addition of 70, 130, 180, and 200 c.c. These fractions melted at 97—100°, 97—100°, 90—98°, and 85—95° respectively, and each was raised to *ca.* 100—103° by repeated recrystallisation from alcohol.

(*c*) The solution was made alkaline with aqueous sodium hydroxide, and the precipitated 4-chloro-nitro-3-methylquinolines were collected, washed with water, and dried (7·8 g., 70%; m. p. 94—97°). The solid was steam-distilled for 36 hours. The solid distillate was collected, washed, and dried (2·5 g.; m. p. 110—130°), and two recrystallisations from alcohol gave *4-chloro-5-nitro-3-methylquinoline* (1·1 g.;

15% of the mixture) in almost colourless needles, m. p. 141·5° (Found: C, 54·2; H, 3·3. $C_{10}H_7O_3N_2Cl$ requires C, 53·9; H, 3·2%). A farther fraction, m. p. 100—103° (0·7 g.), was obtained from the mother-liquors. The solid residue from the steam-distillation was collected, washed, dried (2·2 g.; m. p. 105—115°), and recrystallised twice from alcohol. 4-Chloro-8-nitro-3-methylquinoline (0·75 g.; 11% of the mixture) separated in almost colourless needles, m. p. and mixed m. p., with a specimen prepared from 8-nitro-4-hydroxy-3-methylquinoline, 125°. A further fraction, m. p. 100—103° (0·8 g.), was obtained from the mother-liquors.

Proof of the Constitution of 4-Chloro-6-nitro-3-methylquinoline.—*Ethyl 6-nitro-4-hydroxy-3-methylquinoline-2-carboxylate* (cf. Steck, Hallock, and Holland, *J. Amer. Chem. Soc.*, 1946, **68**, 131). A solution of *p*-nitroaniline (10·0 g.) and ethyl ethoxalylpropionate (10·1 g.) in benzene (120 c.c.) was boiled under reflux for 24 hours and, after cooling, filtered from excess of *p*-nitroaniline (7·8 g.; m. p. 148°). The filtrate was washed with 0·5*N*-hydrochloric acid (3 × 60 c.c.), water (100 c.c.), 0·5*N*-aqueous sodium hydroxide (3 × 60 c.c.), and water (3 × 100 c.c.). The solution was then dried (Na_2SO_4), and the solvent removed by distillation. The residual oil was added slowly to boiling phenyl ether (100 c.c.), and boiling was continued for 10 minutes. After cooling, the precipitated *ethyl 6-nitro-4-hydroxy-3-methylquinoline-2-carboxylate* (3·0 g.) was collected, washed with light petroleum (b. p. 60—80°), and recrystallised from alcohol. It separated in straw-coloured needles, m. p. 274—276° (Found: C, 56·6; H, 4·3. $C_{13}H_{12}O_5N_2$ requires C, 56·5; H, 4·4%).

6-Nitro-4-hydroxy-3-methylquinoline-2-carboxylic acid (cf. Steck, Hallock, and Holland, *loc. cit.*). Ethyl 6-nitro-4-hydroxy-3-methylquinoline-2-carboxylate (2·8 g.) was boiled with 5% aqueous sodium hydroxide (50 c.c.) for three hours. The cooled, red solution was acidified with concentrated hydrochloric acid, and the precipitate collected and washed with water. Recrystallisation from alcohol gave *6-nitro-4-hydroxy-3-methylquinoline-2-carboxylic acid* (2·3 g.) in yellow prisms, m. p. >360° (Found: C, 53·4; H, 2·9. $C_{11}H_8O_5N_2$ requires C, 53·2; H, 3·2%).

4-Chloro-6-nitro-3-methylquinoline (cf. Kermack and Weatherhead, *J.*, 1940, 1168). A mixture of 6-nitro-4-hydroxy-3-methylquinoline-2-carboxylic acid (1·1 g.), copper bronze (0·5 g.), and quinoline (10 c.c.) was boiled under reflux for 6 hours. The cooled solution was filtered, and the solid residue extracted with ethyl alcohol (50 c.c.). Evaporation of the extract to dryness gave 6-nitro-4-hydroxy-3-methylquinoline (0·1 g.; m. p. >360°) as a yellow-brown powder. The quinoline filtrate was added to water (200 c.c.) and steam-distilled until no quinoline remained. Evaporation of the residual aqueous solution to dryness gave a further yield of 6-nitro-4-hydroxy-3-methylquinoline (0·1 g.; m. p. >360°) as a yellow-brown powder.

The total product (0·2 g.) was converted into the 4-chloro-compound as already described; authentic 4-chloro-6-nitro-3-methylquinoline (0·05 g.) was obtained in fawn needles, m. p. 171·5°.

4-Chloro-6-amino-3-methylquinoline. 4-Chloro-6-nitro-3-methylquinoline (1·6 g.) and Raney-nickel sludge (2 c.c.) were suspended in ethyl alcohol (100 c.c.) and shaken with hydrogen at atmospheric pressure until absorption of hydrogen ceased (approximately 500 c.c.). The catalyst was filtered off and washed with alcohol, and the filtrate and washings were evaporated to dryness. Crystallisation of the residue from alcohol gave *4-chloro-6-amino-3-methylquinoline* (0·5 g.) in grey plates, m. p. 228° (Found: C, 62·4; H, 5·0. $C_{10}H_9N_2Cl$ requires C, 62·3; H, 4·7%). The amine dissolves in alcohol to give a yellow solution with a violet fluorescence.

4 : 6-Dichloro-3-methylquinoline. Copper sulphate (2·8 g.) and sodium chloride (0·95 g.) were dissolved in water (10 c.c.) at 55—60°, and a solution of sodium metabisulphite (1·4 g.) in water (2·5 c.c.) was added. The mixture was cooled to 10—15°, and the precipitated cuprous chloride was collected, washed with water, and dissolved in a mixture of water (2·0 c.c.) and concentrated hydrochloric acid (2·0 c.c.). 4-Chloro-6-amino-3-methylquinoline (0·06 g.) was dissolved in water (0·15 c.c.)–concentrated hydrochloric acid (0·15 c.c.) and the solution cooled to 0—5°. A solution of sodium nitrite (0·05 g.) in water (0·15 c.c.) was added, and after a few minutes the combined solution was added to the cuprous chloride solution (0·3 c.c.) at 60°. After 10 minutes at room temperature and 15 minutes on the boiling water-bath the mixture was added to water (50 c.c.), made just alkaline with aqueous sodium hydroxide, and steam-distilled. The white solid distillate was collected, and crystallisation from aqueous alcohol gave 4 : 6-dichloro-3-methylquinoline (0·014 g.) in colourless needles, m. p. 118—119°. This m. p. is identical with that quoted by Breslow *et al.* (*J. Amer. Chem. Soc.*, 1946, **68**, 1233).

Proof of the Constitution of 4-Chloro-5-nitro-3-methylquinoline.—*4 : 5-Dichloro-3-methylquinoline.* This compound was prepared from 4-chloro-5-nitro-3-methylquinoline (0·32 g.) as already described for the preparation of the 4 : 6-dichloro-compound. It (0·04 g.) separated from aqueous alcohol in colourless, feathery needles, m. p. 70—71°. The melting point was not depressed on admixture with an authentic specimen, prepared as described by Steck, Hallock, and Holland (*J. Amer. Chem. Soc.* 1946, **68**, 382) from ethyl ethoxalylpropionate and *m*-chloroaniline.

Proof of the Constitution of 4-Chloro-8-nitro-3-methylquinoline.—*4-Chloro-8-amino-3-methylquinoline.* 4-Chloro-8-nitro-3-methylquinoline (1·3 g.) was reduced as described above for the preparation of the 6-amino-compound, and gave *4-chloro-8-amino-3-methylquinoline* (0·7 g.) in colourless needles, m. p. 111° (from aqueous alcohol) (Found: C, 62·4; H, 4·6. $C_{10}H_9N_2Cl$ requires C, 62·3; H, 4·7%).

4 : 8-Dichloro-3-methylquinoline. 4-Chloro-8-amino-3-methylquinoline (0·20 g.) underwent the Sandmeyer reaction as described above for the 4 : 6-dichloro-compound. 4 : 8-Dichloro-3-methylquinoline (0·04 g.) separated from aqueous alcohol in slightly pink, feathery needles, m. p. 98°. The melting point was not depressed on admixture with an authentic specimen, prepared from *o*-chloroaniline and ethyl ethoxalylpropionate as described by Breslow *et al.* (*J. Amer. Chem. Soc.*, 1946, **68**, 1233).

Ethyl 5(or 7)-Nitro-4-hydroxy-3-methylquinoline-2-carboxylate.—The interaction of ethyl ethoxalylpropionate (20·2 g.) and *m*-nitroaniline (15·0 g.), as described above for the preparation of the 6-nitro-ester,

gave a mixture of ethyl 5- and 7-nitro-4-hydroxy-3-methylquinoline-2-carboxylates (3·0 g.; m. p. 220—230°), which was recrystallised repeatedly from alcohol. *Ethyl 5(or 7)-nitro-4-hydroxy-3-methylquinoline-2-carboxylate* separated in straw-coloured needles, m. p. 268—269° (Found: C, 56·3; H, 4·4. $C_{13}H_{12}O_5N_2$ requires C, 56·5; H, 4·4%).

6-Nitro-4-p-chloroanilino-3-methylquinoline.—An intimate mixture of 4-chloro-6-nitro-3-methylquinoline (3·5 g.) and *p*-chloroaniline (2·1 g.) was heated in a wax-bath. Reaction occurred at 120° and the temperature rose quickly to 150°, where it was maintained for five minutes. When cold, the solid product was powdered, dissolved in hot glacial acetic acid (150 c.c.), and poured into water (600 c.c.). The precipitated *6-nitro-4-p-chloroanilino-3-methylquinoline* (4·0 g.) was collected, washed with water, and dried. Crystallisation from toluene gave bright-yellow needles, m. p. 173—174° (Found: C, 61·4; H, 3·8. $C_{16}H_{12}O_2N_3Cl$ requires C, 61·3; H, 3·8%).

6-Amino-4-p-chloroanilino-3-methylquinoline. A solution of stannous chloride (20·0 g.) in concentrated hydrochloric acid (20 c.c.) was added to a solution of 6-nitro-4-*p*-chloroanilino-3-methylquinoline (4·0 g.) in glacial acetic acid (40 c.c.). The mixture was heated for one hour on a boiling water-bath and then left at room temperature for 48 hours. The solution was made strongly alkaline with 50% aqueous sodium hydroxide, and boiled until the precipitated yellow stannichloride had decomposed. The grey residue was collected, boiled with 25% aqueous sodium hydroxide (100 c.c.) for five minutes, filtered off, washed with dilute aqueous sodium hydroxide and much water, and dried. Crystallisation from toluene gave *6-amino-4-p-chloroanilino-3-methylquinoline* (1·8 g.) in fawn prisms, m. p. 229—230° (Found: C, 68·1; H, 4·9. $C_{16}H_{14}N_3Cl$ requires C, 67·7; H, 4·9%). The amine dissolves in alcohol and in toluene to give yellow solutions with a violet fluorescence. The *picrate* separated from alcohol in golden plates, m. p. 238—239° (Found: C, 51·6; H, 3·4. $C_{16}H_{14}N_3Cl,C_6H_3O_7N_3$ requires C, 51·5; H, 3·3%).

Reaction between Aniline and Ethyl Ethoxalylpropionate at High Temperatures.—Aniline (2·32 g., 0·025 mole) and ethyl ethoxalylpropionate (5·05 g., 0·025 mole) were boiled together under reflux for two minutes. After cooling overnight, the solid product was filtered off, washed with methyl alcohol, and dried. Recrystallisation from ethyl alcohol gave 2:5-diketo-4-phenylimino-1-phenyl-3-methylpyrrolidine (3·70 g.) in glistening yellow plates, m. p. 158° (Found: C, 73·2; H, 5·2; N, 10·2. Calc. for $C_{19}H_{16}O_2N_2$: C, 73·4; H, 5·0; N, 10·1%). Wislicenus and Spiro (*loc. cit.*) reported m. p. 158—160°.

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431. *The Chemistry of Carcinogenic Nitrogen Compounds. Part V. Angular Hydroxybenzacridines and Hydroxydibenzacridines.*

By NG.PH. BUU-HOÏ.

A number of new 1:2- and 3:4-benzacridines containing hydroxy- or alkoxy-groups have been prepared for biological examination; similar compounds in the three biangular dibenzacridine series were also synthesised. Several allyloxy-benzacridines were rearranged by the Claisen method. The thermal condensation of naphthols with aromatic aldehydes and amines to give benzacridines was more closely investigated.

A number of carcinogenic polycyclic hydrocarbons are known to undergo metabolic conversion into the corresponding hydroxy-compounds. Polycyclic nitrogen-containing carcinogens have not yet been studied in this respect, but their close structural analogy with isocyclic hydrocarbons suggests that their metabolism might follow a similar pattern. To obtain some experience with compounds similar to the expected metabolites, and in view of the increased interest attached to hydroxy-acridines, a series of hydroxy-derivatives of 1:2- and 3:4-benzacridine has now been synthesised.

Many such compounds, mostly in the 3:4-benzacridine series, have already been reported; some in very scanty detail. Baezner (*Ber.*, 1904, **37**, 3080) prepared 3′-hydroxy-3:4-benzacridine by reduction of a mixture of *o*-nitrobenzyl chloride and 2:7-dihydroxynaphthalene, and by condensing *N*-*o*-aminobenzylaniline with the latter. Similar reduction of 2-nitrobenzyl chloride and 2:6-dihydroxynaphthalene yielded the isomeric 2′-hydroxy-3:4-benzacridine (Baezner and Gueorguieff, *Ber.*, 1906, **39**, 2445) and the same authors (*ibid.*, p. 2439) prepared 8-hydroxy-3:4-benzacridine by acid hydrolysis of the corresponding 8-amino-compound. More recently, the preparation of the 2-hydroxy-compound from 3-amino-1-naphthol was briefly mentioned in a patent, without any description of the procedure or the product (D.R.P. 384,790/1922). Saftien (*Ber.*, 1925, **58**, 1958) obtained 7-methoxy-3:4-benzacridine by decarboxylation of the 5-carboxylic acid from the Fries condensation of 4:5-benzcoumaran-2:3-dione with *p*-anisidine, no demethylation however being attempted.

We found that 7-methoxy-3:4-benzacridine was very easily prepared by the Ullmann–Fettvadjian reaction (*Ber.*, 1903, **36**, 1029) from 2-naphthol, *p*-anisidine, and paraformaldehyde; subsequent demethylation to 7-hydroxy-3:4-benzacridine was conveniently achieved by means

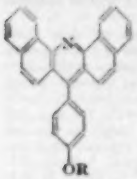
of pyridine hydrochloride; 7-hydroxy-2'-*tert.*-butyl- and -2'-*tert.*-amyl-3 : 4-benzacridine were similarly obtained from 6-*tert.*-butyl- and 6-*tert.*-amyl-2-naphthol. Homologues of 7-hydroxy-3 : 4-benzacridine having substituents in the *meso*-position were prepared from *N*-*p*-methoxyphenyl-2-naphthylamine by a modified Bernthsen reaction (Buu-Hoï, *J.*, 1946, 792; 1949, 670), and demethylation of the intermediary methyl ethers: 7-hydroxy-5-methyl-, -5-ethyl-, and -5-*iso*propyl-3 : 4-benzacridine were thus obtained.

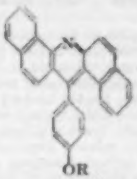
In the 1 : 2-benzacridine series, the Ullmann–Fettvadjian reaction with 1-naphthol was much less satisfactory than with 2-naphthol, but the 7-hydroxy-compound was nevertheless obtained *via* 7-methoxy-1 : 2-benzacridine.

The allyl ether of 7-hydroxy-3 : 4-benzacridine readily underwent the Claisen rearrangement, 7-hydroxy-6-allyl-3 : 4-benzacridine being formed quantitatively after some minutes in boiling dimethylaniline. This high reactivity of the 6-position makes it analogous to the α-position in 2-naphthol and 2-anthrol.

It was found, as previously reported by others, that benzacridines obtained from 2-naphthol by means of the Ullmann (*Ber.*, 1900, **33**, 907) and similar reactions (Senier and Austin, *J.*, 1907, **91**, 1237) have the 3 : 4-benzacridine structure and not the alternative 2 : 3-benzacridine, as derivatives of the latter nucleus give a violet colour with sulphuric acid and deep-red to violet salts (Schöpff, *Ber.*, 1894, **27**, 2843) instead of the corresponding yellow-orange colour observed with 3 : 4-benzacridines.

Senier and Austin (*loc. cit.*) prepared 5-*p*-methoxyphenyl-1 : 2-8 : 9-dibenzacridine (I; R = Me) by adding anisaldehyde to a boiling mixture of 1-naphthylamine and 1-naphthol. Contrary to Senier and Austin's claims, an extension of this reaction to mixtures of 2-naphthol with 1- and 2-naphthylamine was possible, and allowed of the preparation of 5-*p*-methoxyphenyl-1 : 2-6 : 7- (II; R = Me) and -3 : 4-6 : 7-dibenzacridine (III; R = Me). Pyridine hydrochloride demethylation of Senier and Austin's compound and its two isomers gave the


(I.)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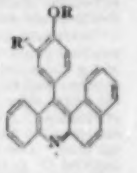
(IV.)

corresponding phenols, high-melting substances similar to 5-*p*-hydroxyphenylacridine prepared by Landauer (*Bull. Soc. chim.*, 1904, **31**, 1091) from *p*-hydroxybenzoic acid by the Bernthsen reaction. Furthermore, we have found that anisaldehyde reacted with mixtures of 2-naphthol and aniline or its homologues, the intermediary 5 : 10-dihydroacridines being oxidised by prolonged heating in air. 5-*p*-Methoxyphenyl-3 : 4-benzacridine (IV; R = Me, R' = H) and its 7-methyl, 7 : 9-dimethyl, 8 : 9-dimethyl, and 7-phenyl homologues were thus prepared; demethylation gave 5-*p*-hydroxyphenyl-3 : 4-benzacridine (IV; R = R' = H) and homologues. The allyl ethers of these phenols readily underwent the Claisen rearrangement, although much less rapidly than in the case of 7-hydroxy-3 : 4-benzacridine. 5-(4-Hydroxy-3-allylphenyl)-3 : 4-benzacridine (IV; R = H, R' = CH_2·CH:CH_2) and its 7-methyl and 8 : 9-dimethyl homologues were thus obtained.

Experimental.

7-Methoxy-3 : 4-benzacridine.—Paraformaldehyde (1·5 g.) was added in small portions to a boiling mixture of *p*-anisidine (15 g.) and 2-naphthol (15 g.). After the violent reaction had subsided, the product obtained was boiled in the air for some minutes, and then vacuum-distilled. The fraction, b. p. 290—300°/18 mm. (16 g.), solidified on being left in ethanol. After two recrystallisations from this solvent, long silky, pale-yellow needles, m. p. 158°, were obtained (Saftien, *loc. cit.*, gave m. p. 157°). The corresponding picrate formed, from nitrobenzene, shiny, silky, orange-yellow prisms, m. p. 295—296° (decomp.).

7-Hydroxy-3 : 4-benzacridine.—A mixture of the methoxy-compound (10 g.) and pyridine hydrochloride (50 g.) was refluxed for 10 minutes, the supernatant layer completely disappearing. After cooling, hot water (100 c.c.) was added, and the orange precipitate of 7-hydroxy-3 : 4-benzacridine hydrochloride collected and washed with water. Basification with dilute aqueous ammonia gave the base, which was dried and recrystallised from nitrobenzene. *7-Hydroxy-3 : 4-benzacridine* (8 g.) formed shiny, greenish-yellow needles, m. p. 310°, which gave a deep-yellow solution in aqueous sodium hydroxide (Found: C, 82·9; H, 4·4. $C_{17}H_{11}ON$ requires C, 83·2; H, 4·4%).

7-Hydroxy-6-allyl-3 : 4-benzacridine.—The 7-hydroxy-benzacridine (2·5 g.) was treated with potassium hydroxide (1 g.) in ethanol, and the resulting solution refluxed for five minutes with allyl bromide (1·5 g.). The solvent was removed in vacuum, water added to the residue, and the cloudy suspension left overnight. *7-Allyloxy-3 : 4-benzacridine* thus obtained (2·5 g.) crystallised from light petroleum in long silky, pale-yellow needles, m. p. 92°, extremely soluble in ethanol (Found: N, 4·6. $C_{20}H_{15}ON$ requires N, 4·9%). The corresponding *picrate* formed, from xylene, orange-yellow needles, m. p. 260—262° (decomp. >240°) (Found: N, 10·6. $C_{32}H_{18}O_8N_4$ requires N, 10·9%). A solution of this allyl ether (2 g.) in anhydrous dimethylaniline (10 c.c.) was refluxed for one hour, and the solvent removed in vacuum; the solid obtained was washed with methanol, and recrystallised from pyridine, giving readily sublimable, silky yellowish needles (1·6 g.), m. p. 288—289° (decomp.), of *7-hydroxy-6-allyl-3 : 4-benzacridine* which gave an orange solution in ethanolic potassium hydroxide (Found: C, 84·2; H, 5·8. $C_{20}H_{15}ON$ requires C, 84·2; H, 5·2%).

7-Hydroxy-2'-tert.-butyl-3 : 4-benzacridine.—This was obtained by demethylation of the crude orange-red viscous distillate (b. p. >300°/18 mm.) from the Ullmann–Fettvadjian reaction of *6-tert.*-butyl-2-naphthol (2 g.), *p*-anisidine (2 g.), and paraformaldehyde (0·5 g.). The hydrochloride was orange-yellow, and the *base* (0·6 g.) formed, from xylene, pale-yellow needles, m. p. 288° (Found: C, 83·6; H, 6·5. $C_{21}H_{19}ON$ requires C, 83·7; H, 6·3%).

7-Hydroxy-2'-tert.-amyl-3 : 4-benzacridine.—This, prepared in the same way as the *tert.*-butyl compound, formed, from xylene, shiny yellowish needles, m. p. 280—281° (Found: C, 83·5; H, 6·8. $C_{22}H_{21}ON$ requires C, 83·8; H, 6·6%). These two hydroxy-benzacridines with a free 6-position, shared with 7-hydroxy-3 : 4-benzacridine the property of reacting with 2 : 3-dichloro-1 : 4-naphthaquinone in pyridine solution to give high-melting, sublimable, orange-red products (cf. Eistert, *Ber.*, 1947, **80**, 52).

7-Methoxy-1 : 2-benzacridine.—A boiling mixture of 1-naphthol (15 g.) and *p*-anisidine (15 g.) was treated with paraformaldehyde (1·5 g.). Vacuum-distillation of the product gave a resinous portion (3 g.), b. p. 280—310°/16 mm., which solidified when left with ethanol; it gave after recrystallisation from this solvent, fluffy, shiny, pale-yellow needles, m. p. 155° (Found: C, 83·3; H, 5·2. $C_{18}H_{13}ON$ requires C, 83·4; H, 5·0%). Its *picrate* formed, from nitrobenzene, silky orange-yellow, sublimable prisms, m. p. 246—248° (decomp.) (Found: N, 11·2. $C_{18}H_{13}ON,C_6H_3O_7N_3$ requires N, 11·5%).

7-Hydroxy-1 : 2-benzacridine.—This *acridine* was obtained in almost quantitative yield from the demethylation of the 7-methoxy-base, and formed, from nitrobenzene, fine pale-yellow needles, m. p. 217—218° (Found: C, 83·1; H, 4·4. $C_{17}H_{11}ON$ requires C, 83·2; H, 4·4%), giving yellow alkaline solutions and an orange hydrochloride.

7-Methoxy-5-methyl-3 : 4-benzacridine.—*N-p*-Methoxyphenyl-2-naphthylamine used in this work was best prepared in the following way: a mixture of 2-naphthol (45 g.), *p*-anisidine (40 g.), and iodine (0·2 g.) was gently refluxed for 20 hours; the product was taken up in benzene, washed with dilute aqueous sodium hydroxide, dried (Na_2SO_4) and vacuum-distilled after removal of the solvent, giving the amine (60 g.), b. p. 263—265°/16 mm. This (10 g.) was heated under reflux for 18 hours with acetic anhydride (7 g.) and fused zinc chloride (10 g.); and the hot product was treated with toluene and concentrated aqueous sodium hydroxide (Buu-Hoï, *loc. cit.*), leaving a large residue of insoluble charred material. The toluene solution was dried (Na_2SO_4), the solvent removed, and the residue vacuum-distilled (b. p. *ca.* 285—300°/16 mm.). After repeated recrystallisations from methanol, *7-methoxy-5-methyl-3 : 4-benzacridine* (0·5 g.) formed silky, pale-yellow needles, m. p. 144° (Found: C, 83·3; H, 5·6. $C_{19}H_{15}ON$ requires C, 83·5; H, 5·5%), and gave a picrate crystallising from nitrobenzene in silky, orange-yellow prisms, m. p. 254—256° (decomp.).

7-Hydroxy-5-methyl-3 : 4-benzacridine.—Prepared by demethylation of the 7-methoxy-compound, this *acridine* formed, from nitrobenzene, readily sublimable, pale yellow needles, m. p. 290—291° (decomp.), which gave yellow solutions in alkali (Found: C, 83·5; H, 5·2. $C_{18}H_{13}ON$ requires C, 83·4; H, 5·0%). *7-Hydroxy-5-ethyl-3 : 4-benzacridine*, similarly prepared by demethylation of the crude, distilled product from *N-p*-methoxyphenyl-2-naphthylamine (5 g.), propionic anhydride (5 g.), and zinc chloride (5 g.), formed yellow needles from xylene, sublimating above 275—280° and charring at 286—290° (Found: C, 83·2; H, 5·4. $C_{19}H_{15}ON$ requires C, 83·5; H, 5·5%). *7-Hydroxy-5-isopropyl-3 : 4-benzacridine*, obtained by replacement of propionic anhydride in the previous synthesis by *iso*butyric acid, formed fine yellow needles, from nitrobenzene, which darkened and sublimed above 275°, and decomposed above 285—286° (Found: C, 83·5; H, 5·8. $C_{20}H_{17}ON$ requires C, 83·6; H, 5·9%).

5-p-Methoxyphenyl-1 : 2-6 : 7-dibenzacridine.—To a boiling mixture of 2-naphthol (5 g.) and 1-naphthylamine (5 g.), anisaldehyde (4 g.) was cautiously added, and the product boiled for a further five minutes and then vacuum-distilled; the portion, b. p. >350°/18 mm., solidified on trituration with ethanol, and formed fine, almost colourless needles (1·5 g.), m. p. 202°, of the *acridine* from benzene (Found: N, 3·4. $C_{32}H_{21}ON$ requires N, 3·6%). The corresponding picrate crystallised from xylene in orange-yellow needles, m. p. 272—273°. *5-p-Hydroxyphenyl-1 : 2-6 : 7-dibenzacridine* formed readily sublimable, greenish-yellow needles, m. p. 301°, from nitrobenzene (Found: C, 87·1; H, 4·6. $C_{31}H_{19}ON$ requires C, 87·3; H, 4·5%); this compound gave a deep yellow colour in alcoholic sodium hydroxide solution; its orange-yellow hydrochloride was only sparingly soluble in molten pyridine hydrochloride.

5-p-Methoxyphenyl-3 : 4-6 : 7-dibenzacridine.—Obtained in similar yield from β-naphthol (5 g.), β-naphthylamine (5 g.), and anisaldehyde (4 g.), this *dibenzacridine* formed long silky, pale yellow, sublimable needles, m. p. 274—275°, from benzene (Found: N, 3·4. $C_{32}H_{21}ON$ requires N, 3·6%). *5-p-Hydroxyphenyl-3 : 4-6 : 7-dibenzacridine* was sparingly soluble in nitrobenzene, and from this solvent formed fine deep-yellow, sublimable needles, m. p. 370—372° (Found: C, 87·0; H, 4·7. $C_{31}H_{19}ON$ requires C, 87·3; H, 4·5%).

5-p-Hydroxyphenyl-1 : 2-8 : 9-dibenzacridine.—This *acridine* formed large, transparent, yellowish crystals, m. p. 248°, from aqueous acetone (Found: C, 87·2; H, 4·8. $C_{31}H_{19}ON$ requires C, 87·3; H, 4·5%). Its methyl ether was prepared in 30% yield by Senier and Austin's method (*loc. cit.*).

5-p-Methoxyphenyl-3 : 4-benzacridine.—Anisaldehyde (15 g.) was cautiously dropped into a boiling mixture of β-naphthol (20 g.) and aniline (15 g.); after a further 5 minutes' boiling in the air, the product was vacuum-fractionated. The fraction, b. p. *ca.* 300—320°/14 mm. (8 g.), gave, after two crystallisations from ethanol, pale-yellow, silky needles, m. p. 181° (Found : N, 4·0. $C_{24}H_{17}ON$ requires N, 4·1%). The corresponding *picrate* formed silky orange needles, m. p. 253—254°, from toluene (Found : N, 9·6. $C_{30}H_{20}O_8N_4$ requires N, 9·9%).

5-p-Hydroxyphenyl-3 : 4-benzacridine.—This *compound* formed readily sublimable, shiny, pale yellow leaflets, m. p. 306°, from nitrobenzene (Found : C, 85·7; H, 4·8. $C_{23}H_{15}ON$ requires C, 85·9; H, 4·7%).

5-p-Allyloxyphenyl-3 : 4-benzacridine.—The 5-p-*allyloxyphenyl* derivative, prepared from the potassium salt of the hydroxyphenyl compound and allyl bromide in alcoholic solution, crystallised from acetone in large pale-yellow tablets, m. p. 176—177° (Found : N, 3·8. $C_{26}H_{19}ON$ requires N, 3·9%); its picrate formed silky orange-yellow needles, m. p. 223—224°, from toluene.

5-(4-Hydroxy-3-allylphenyl)-3 : 4-benzacridine.—This was obtained by refluxing a dimethylaniline solution of the foregoing allyl ether for 12 hours; it formed fine pale-yellow prisms, m. p. 255°, from acetone, and gave yellow solutions in alcoholic sodium hydroxide (Found : C, 86·2; H, 5·3. $C_{26}H_{19}ON$ requires C, 86·4; H, 5·2%).

5-p-Methoxyphenyl-7-methyl-3 : 4-benzacridine.—This compound (10 g.), obtained as above from 2-naphthol (20 g.), *p*-toluidine (18 g.), and anisaldehyde (15 g.), had b. p. 325—330°/14 mm., and formed pale yellow, silky, sublimable needles, m. p. 231—232°, from much ethanol (Found : N, 4·0. $C_{25}H_{19}ON$ requires N, 4·0%); its *picrate* formed orange prisms, m. p. 249—250°, from toluene (Found : N, 9·6. $C_{31}H_{22}O_8N_4$ requires N, 9·5%).

5-p-Hydroxyphenyl-7-methyl-3 : 4-benzacridine.—The *p-hydroxyphenyl* compound, obtained in theoretical yield, crystallised from nitrobenzene in long silky, pale-yellow, readily sublimable needles, m. p. 326—327°, which gave greenish-yellow solutions with alcoholic sodium hydroxide (Found : C, 86·0; H, 5·2. $C_{24}H_{17}ON$ requires C, 85·9; H, 5·0%).

5-p-Allyloxyphenyl-7-methyl-3 : 4-benzacridine.—The *allyloxy*-compound formed long, silky, pale-yellow needles, m. p. 171°, from ethanol (Found : N, 3·5. $C_{27}H_{21}ON$ requires N, 3·7%); its rearrangement product, *5-(4-hydroxy-3-allylphenyl)-7-methyl-3 : 4-benzacridine*, crystallised from nitrobenzene in shiny yellowish needles, m. p. 243—244° (Found : C, 86·2; H, 5·7. $C_{27}H_{21}ON$ requires C, 86·4; H, 5·6%); the *4-allyloxyphenyl-3-allyl* compound formed fine colourless needles, m. p. 131—132°, from methanol (Found : N, 3·2. $C_{30}H_{25}ON$ requires N, 3·3%), the picrate of which separated from ethanol in deep-orange needles, m. p. 209°.

5-p-Methoxyphenyl-7 : 9-dimethyl-3 : 4-benzacridine.—This could not be obtained in a pure state directly by the condensation of anisaldehyde with 2-naphthol and 2 : 4-dimethylaniline, which yielded at the same time a great quantity of a high-melting impurity believed to be the corresponding 5 : 10-dihydroacridine. It was therefore prepared by methylation of the hydroxy-compound described below, and formed pale-yellow needles, m. p. 177—178°, from ethanol (Found : C, 85·6; H, 5·9. $C_{26}H_{21}ON$ requires C, 85·9; H, 5·7%).

5-p-Hydroxyphenyl-7 : 9-dimethyl-3 : 4-benzacridine.—The *5-p-hydroxyphenylbenzacridine* was prepared by heating with pyridine hydrochloride the crude acridine–dihydroacridine mixture described above; it formed sublimable, glinting, pale-yellow needles, m. p. 313—315°, from nitrobenzene (Found : C, 85·8; H, 5·6. $C_{25}H_{19}ON$ requires C, 85·9; H, 5·4%).

5-p-Methoxyphenyl-8 : 9-dimethyl-3 : 4-benzacridine.—This *compound* (8 g.), readily obtained from 2-naphthol (20 g.), 3 : 4-dimethylaniline (15 g.), and anisaldehyde (15 g.), formed long silky, pale-yellow needles, m. p. 208°, from benzene–ethanol (Found : C, 85·6; H, 5·7. $C_{26}H_{21}ON$ requires C, 85·9; H, 5·7%), and gave a picrate which crystallised from benzene in long silky orange needles, m. p. 250°; no higher-melting impurity was obtained in this experiment.

5-p-Hydroxyphenyl-9 : 9-dimethyl-3 : 4-benzacridine.—This *compound* crystallised from nitrobenzene in sublimable, short, yellow prisms, m. p. 306—307° (Found : C, 85·8; H, 5·6. $C_{25}H_{19}ON$ requires C, 85·9; H, 5·4%); its *allyl ether* formed almost colourless needles, m. p. 215°, from ethanol (Found : N, 3·5. $C_{28}H_{23}ON$ requires N, 3·6%), which gave a picrate as silky orange needles, m. p. 238—240° (decomp. above 205°), from ethanol. *5-(4-Hydroxy-3-allylphenyl)-8 : 9-dimethyl-3 : 4-benzacridine* crystallised from xylene in shiny, fine, yellowish prisms, m. p. 216°, giving a yellow solution with aqueous-alcoholic alkalis (Found : C, 86·1; H, 6·2. $C_{28}H_{23}ON$ requires C, 86·3; H, 5·9%).

7-Phenyl-5-p-methoxyphenyl-3 : 4-benzacridine.—Obtained from 2-naphthol (15 g.), 4-aminodiphenyl (19 g.), and anisaldehyde (10 g.), this *acridine* had b. p. >330°/15 mm. and formed iridescent, bright-yellow leaflets, m. p. 164—165°, from ethanol–benzene (Found : C, 87·2; H, 5·0. $C_{30}H_{21}ON$ requires C, 87·5; H, 5·1%); it gave with picric acid an addition compound crystallising from ethanol in orange needles, m. p. 203—204°.

This work is part of a cancer research scheme, carried out under Professor A. Lacassagne, with the financial support of the United States Public Health Service (Federal Security Agency). The author expresses his thanks to the authorities concerned. The phenolic acridines described above are under investigation for possible fungicidal and virucidal activities (especially against hereditary mammary adenocarcinoma in mice).

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432. *The Synthesis of Long-chain Aliphatic Acids from Acetylenic Compounds. Part III. The Synthesis of Linoleic Acid.*

By R. A. Raphael and Franz Sondheimer.

A flexible method for the preparation of the hitherto inaccessible 1 : 4-diacetylenes has been evolved. By this procedure heptadeca-8 : 11-diyne-1-carboxylic acid (V) has been obtained; catalytic partial hydrogenation of this acid furnished a product containing 63% of linoleic acid. A preliminary account of the work has already been given (*Nature*, 1950, **165**, 235).

Long-chain unsaturated acids with an unbranched carbon skeleton occur abundantly in Nature, most commonly in the form of their glycerides (Hilditch, "The Chemical Constitution of Natural Fats," Chapman and Hall, London, 1947; Ralston, "Fatty Acids and their Derivatives," John Wiley, New York, 1948; Markley, "Fatty Acids," Interscience Publishers, New York, 1947). Usually the acids possess the *cis*-configuration about the double bonds. Synthetic investigations of these acids have been confined almost exclusively to the monoethylenic compounds and, until recently, the routes employed could be classified as variants of four procedures, *i.e.* the Robinson–Robinson keto-ester method (Robinson and Robinson, *J.*, 1925, 175; 1926, 2204; 1930, 745; Kapp and Knoll, *J. Amer. Chem. Soc.*, 1943, **65**, 2062), the Noller bromo-aldehyde method (Noller and Bannerot, *J. Amer. Chem. Soc.*, 1934, **56**, 1563; Baudart, *Compt. rend.*, 1943, **217**, 399), the Baudart acyloin method (*Compt. rend.*, 1945, **220**, 404), and the recent Bowman method (*J.*, 1950, 177). None of these schemes is of general application, and mixtures of *cis*–*trans*-isomers are always obtained.

The only general reaction available which produces nearly pure *cis*-ethylenic compounds is the catalytic partial hydrogenation of the corresponding acetylenic compounds (for references and discussion, see Raphael and Sondheimer, *J.*, 1950, 115; Sondheimer, *J.*, 1950, 877), and this reaction is obviously capable of being widely utilised for the synthesis of the natural ethylenic acids. Although an isolated example of the synthesis of one of the requisite acetylenic acids has been recorded (Bhattacharya, Saletore, and Simonsen, *J.*, 1928, 2678) it is only recently that an elegant general method has been developed by Strong and his collaborators (*J. Amer. Chem. Soc.*, 1948, **70**, 1699, 3391; cf. Newman and Wotiz, *ibid.*, 1949, **71**, 1292), which provides a ready synthesis of long-chain acetylenic acids of the general formula (I):

$$CH_3\cdot[CH_2]_m\cdot C{\equiv}CH + I\cdot[CH_2]_n\cdot Cl \xrightarrow{NaNH_2} CH_3\cdot[CH_2]_m\cdot C{\equiv}C\cdot[CH_2]_n\cdot Cl \xrightarrow[\text{hydrolysis}]{NaCN} CH_3\cdot[CH_2]_m\cdot C{\equiv}C\cdot[CH_2]_n\cdot CO_2H \quad (I.)$$

Catalytic partial hydrogenation of (I) readily furnishes the corresponding *cis*-ethylenic acid.

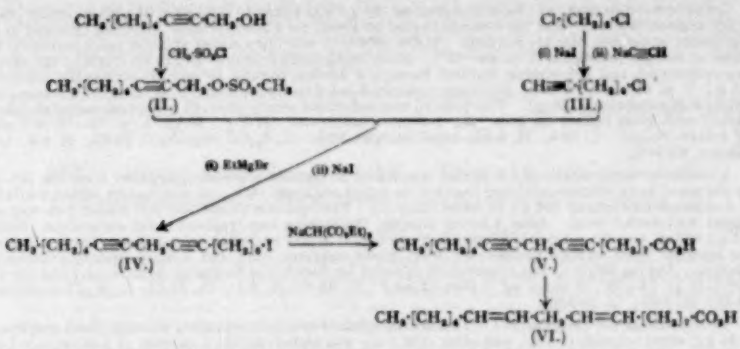
A great many natural polyethylenic acids contain the grouping *cis* : *cis*-$CH{=}CH\cdot CH_2\cdot CH{=}CH$·. One of the most important members of this class is linoleic acid (heptadeca-8 : 11-diene-1-carboxylic acid) (VI), the characteristic acid constituent of the semi-drying oils; the substance derives added interest as an essential food factor (Rosenberg, "Chemistry and Physiology of the Vitamins," Interscience Publishers, New York, 1932, p. 531), and an antibiotic (Riley and Miller, *Arch. Biochem.*, 1948, **18**, 13). Although attempts have been made to synthesise this acid by classical methods, the results have not been encouraging (Noller and Girvin, *J. Amer. Chem. Soc.*, 1937, **59**, 606; Baudart, *Bull. Soc. chim.*, 1944, **11**, 336).

The problem of the acetylenic approach resolves itself into the synthesis of the 1 : 4-diacetylenic acid (V). The scanty literature on 1 : 4-diacetylenes reveals their comparative inaccessibility. A few hydrocarbons of this type had been made by the reaction of substituted propargyl bromides with sodium acetylides at 140°; the yields were poor, however, since the reactivity of the methylene group situated between the two triple bonds resulted in further alkylation of the 1 : 4-diyne produced (Tchao Yin Lai, *Bull. Soc. Chim.*, 1933, **53**, 1533, 1537; Grignard and Lapayre, *ibid.*, 1928, **43**, 141; *Compt. rend.*, 1931, **192**, 250).

It was therefore decided to utilise the ready alkylation of an acetylenic Grignard reagent by means of an alkyl sulphonate (Gilman and Beaber, *J. Amer. Chem. Soc.*, 1923, **45**, 839; Truchet, *Ann. Chim.*, 1931, **16**, 309; Johnson, Schwartz, and Jacobs, *J. Amer. Chem. Soc.*, 1938, **60**, 1882, 1885).

An ethereal solution of the Grignard complex of 8-chloro-oct-1-yne (III) (prepared by the action of sodium acetylide on 1-chloro-6-iodohexane) was very slowly added to a boiling ethereal solution of oct-2-yn-1-yl methanesulphonate (II). This procedure ensured that no excess of

Grignard reagent was present at any time to attack the central, activated methylene group of the product, 16-chlorohexadeca-6 : 9-diyne. This reaction constitutes an efficient and flexible



method of obtaining the hitherto little-studied 1 : 4-diacetylenes. Conversion of the diacetylenic chloride into the corresponding iodide (IV) followed by condensation with sodiomalonic ester, hydrolysis, and decarboxylation, finally gave the required heptadeca-8 : 11-diyne-1-carboxylic acid (V) as a white crystalline solid, m. p. 42—43°. Catalytic partial hydrogenation of (V) employing a palladium–calcium carbonate catalyst gave a pale yellow oil; analysis of this oil by the bromination procedure of Brown and Frankel (*J. Amer. Chem. Soc.*, 1938, **60**, 54) showed it to contain 63% of linoleic acid. The resulting tetrabromostearic acid exhibited no depression in melting point on admixture with a sample prepared from natural linoleic acid. Complete hydrogenation of the diacetylenic acid (V) furnished stearic acid, identified as such by comparison with an authentic sample. As the above tetrabromostearic acid has been shown to furnish substantially pure linoleic acid on debromination (Frankel and Brown, *ibid.*, 1943, **65**, 415) the above series of reactions constitutes a complete synthesis of linoleic acid.

Experimental.

(All operations involving acetylenic compounds were carried out under nitrogen.)

Oct-2-yn-1-ol (cf. Tchao Yin Lai, *Bull. Soc. chim.*, 1933, **53**, 682).—To a stirred solution of ethylmagnesium bromide [from magnesium (16·2 g.), ethyl bromide (98 g.), and ether (400 c.c.)] was added rapidly a solution of hept-1-yne (54 g.) in ether (50 c.c.), and the mixture was heated under reflux for 2 hours. Dry gaseous formaldehyde, prepared by heating dry paraformaldehyde (60 g.) to 200°, was then introduced into the cooled solution of heptynylmagnesium bromide by means of a slow current of nitrogen. After the addition the reaction mixture was heated under reflux for a further 30 minutes, and was then decomposed with ice and dilute sulphuric acid. The ethereal layer was separated, washed with sodium hydrogen carbonate solution, and dried ($MgSO_4$), and the solvent removed. Distillation of the residue gave oct-2-yn-1-ol (40 g., 57%), b. p. 98—100°/15 mm., n_D^{20} 1·4559 (Tchao Yin Lai, *loc. cit.*, gives b. p. 98—99°/15 mm., n_D^{17} 1·4585). The high-boiling residue (*ca.* 25 g.) presumably consisted of higher-condensation products of the general formula, $C_5H_{11}\cdot C{\equiv}C\cdot CH_2\cdot[OCH_2]_n\cdot OH$.

Oct-2-yn-1-yl Methanesulphonate (II).—A well-stirred mixture of oct-2-yn-1-ol (36 g.) and methanesulphonyl chloride (40 g., 1 mol.) was cooled to −10° and aqueous sodium hydroxide (25%) added dropwise at such a rate that the temperature did not rise above 5°. When the mixture became alkaline (about 100 c.c. of the alkali solution was needed) it was thoroughly extracted with ether. Evaporation of the washed (water) and dried ($MgSO_4$) ethereal extract followed by fractionation of the residue gave unchanged carbinol (20·5 g.) and *oct-2-yn-1-yl methanesulphonate* (22·1 g.; conversion, 45%; yield, 85%), b. p. 110—112°/0·2 mm., n_D^{20} 1·4610. The employment of two moles of the acid chloride surprisingly occasioned no improvement in conversion (Found: C, 52·5; H, 7·6; S, 14·8. $C_9H_{16}O_3S$ requires C, 52·9; H, 7·9; S, 15·7%).

This reaction could not be carried out by the more usual procedure employing pyridine. When this was attempted the only product obtained, in small yield, was *1-chloro-oct-2-yne*, b. p. 40—41°/0·5 mm., n_D^{20} 1·4590 (Found: C, 66·65; H, 9·05; Cl, 24·3. $C_8H_{13}Cl$ requires C, 66·45; H, 9·05; Cl, 24·5%).

1 : 6-*Dichlorohexane*.—Hexamethylene glycol (59 g.) and dry pyridine (7 c.c.) were melted together and thionyl chloride (20 g.) then added to lower the melting point. To the cooled, stirred mixture thionyl chloride (218 g.) was added at such a rate that the temperature remained at about 25°. After the addition the flask and contents were heated by steam for 2 hours. Ice and water were then carefully added, and the dense, precipitated oil taken up in light petroleum (b. p. 40—60°); this extract

was washed twice with concentrated sulphuric acid and once with sodium hydrogen carbonate solution, dried ($MgSO_4$), and evaporated. The residue on distillation furnished 1 : 6-dichlorohexane (72 g.; 92%), b. p. 99°/28 mm., n_D^{20} 1·4576.

1-*Chloro*-6-*iodohexane*.—1 : 6-Dichlorohexane (65 g.) was added to a solution of sodium iodide (65 g.) in dry acetone (400 c.c.), and the solution heated by steam for 4 hours (violent bumping occurred as the precipitate of sodium chloride formed). Water (600 c.c.) was then added and the precipitated oil was taken up in light petroleum (b. p. 40—60°). After being washed (water) and dried ($MgSO_4$) the extract was evaporated, and the residue distilled through a Dufton column to give (i) unchanged dichloride (18 g.), b. p. 51—53°/0·6 mm., (ii) crude 1-chloro-6-iodohexane (50·3 g.), b. p. 74—79°/0·6 mm., and (iii) 1 : 6-di-iodohexane (28 g.). Fraction (ii) was redistilled slowly through a vacuum-jacketed column packed with glass helices to give pure 1-*chloro*-6-*iodohexane* (41·6 g., 50%), b. p. 73—74°/0·7 mm., n_D^{20} 1·5248 (Found: C, 29·4; H, 5·45; total halogen, 65·8. $C_6H_{12}ClI$ requires C, 29·25; H, 4·9; total halogen, 65·85%).

8-*Chloro*-*oct*-1-*yne* (III).—To a stirred suspension of sodium acetylide [prepared from Na (4·1 g.), by the usual ferric nitrate-catalysed reaction] in liquid ammonia (400 c.c.) was rapidly added a solution of 1-chloro-6-iodohexane (44 g.) in ether (25 c.c.). The reaction vessel was not cooled but was well lagged with cotton wool. After 4 hours' stirring, the lagging was removed, solid ammonium chloride (15 g.) added, and the ammonia allowed to evaporate. Water and ether were added to the residue, and the ethereal layer washed successively with dilute sulphuric acid and sodium hydrogen carbonate solution. Drying ($MgSO_4$) and evaporation followed by distillation furnished 8-*chloro*-*oct*-1-*yne* (19·4 g., 75%), b. p. 73—76°/10 mm., n_D^{20} 1·4590 (Found: C, 66·2; H, 9·1; Cl, 24·75. $C_8H_{13}Cl$ requires C, 66·45; H, 9·05; Cl, 24·5%).

16-*Iodohexadeca*-6 : 9-*diyne* (IV).—To a stirred solution of ethylmagnesium bromide [from magnesium (1·25 g.), ethyl bromide (7·5 g.), and ether (150 c.c.)] was added rapidly a solution of 8-chloro-oct-1-yne (7·5 g.) in ether (10 c.c.). After being stirred for a further 2 hours the resulting solution was transferred to a dropping-funnel and added dropwise during 4 hours to a stirred, vigorously boiling solution of oct-2-yn-1-yl methanesulphonate (22 g.) in ether (100 c.c.). A white solid formed as the reaction proceeded. The resulting suspension was heated under reflux for a further 14 hours, and the cooled reaction mixture was then decomposed by the addition of 2N-sulphuric acid (100 c.c.). Evaporation of the washed (sodium hydrogen carbonate solution) and dried ($MgSO_4$) ethereal layer, and distillation of the residue, gave (i) 1-bromo-oct-2-yne (9·1 g.), b. p. 45—47°/10^{-3} mm., 85°/12 mm., n_D^{20} 1·4830 (Tchao Yin Lai, *Bull. Soc. chim.*, **1933**, **53**, 1533, gives b. p. 92—93°/15 mm., n_D^{20} 1·4927) and (ii) crude 16-chlorohexadeca-6 : 9-diyne (7·3 g.), b. p. 103—115°/10^{-3} mm., n_D^{20} 1·4760. A Lassaigne test indicated that the second fraction contained sulphur as well as chlorine, thus showing that some unchanged methanesulphonate was present. As fractional distillation was impracticable the following procedure was adopted. The crude chlorodiyne, sodium iodide (10 g.), and dry acetone (100 c.c.) were heated under reflux for 5 hours. The solvent was removed under reduced pressure and the residue treated with water and ether; the ethereal layer after being dried, evaporated, and distilled gave (i) 1-*iodo*-*oct*-2-*yne* (1·2 g.), b. p. 53°/10^{-3} mm., n_D^{20} 1·5330 (Found: I, 53·4. $C_8H_{13}I$ requires I, 53·75), and (ii) 16-*iodohexadeca*-6 : 9-*diyne* (5·3 g.), b. p. 120—124°/10^{-3} mm., n_D^{20} 1·4958 (Found: C, 55·4; H, 7·2. $C_{16}H_{25}I$ requires C, 55·8; H, 7·3%).

Heptadeca-8 : 11-*diyne*-1-*carboxylic Acid* (V).—Sodium (0·7 g.) was dissolved in dry ethanol (50 c.c.), ethyl malonate (5·1 g.) was added, and the mixture was heated under reflux for 1 hour. 16-Iodohexadeca-6 : 9-diyne (4 g.) in alcohol (10 c.c.) was rapidly added and the solution heated under reflux for 16 hours. The cooled mixture was treated with a solution of potassium hydroxide (10 g.) in aqueous methanol (100 c.c. of methanol + 5 c.c. of water), and after 40 hours at room temperature most of the solvent was evaporated off *in vacuo*, and water and ether were added. The aqueous layer was acidified (Congo-red) with dilute sulphuric acid, and the precipitated oil extracted with ether. Drying ($MgSO_4$) of the solution and evaporation of the solvent gave a viscous orange oil; this was transferred to a small retort and slowly heated to 140°/10^{-4} mm. Considerable effervescence took place and a pale-yellow oil distilled over which rapidly solidified; an orange resin (*ca.* 3 g.) remained in the retort. Crystallisation of the distillate from light petroleum (b. p. 40—60°) at 0° gave prismatic needles, m. p. 42—43°, of *heptadeca*-8 : 11-*diyne*-1-*carboxylic acid* (930 mg., 29%) (Found: C, 78·8, 78·4; H, 9·7, 9·9. $C_{18}H_{24}O_2$ requires C, 78·25; H, 10·2%).

Stearic Acid.—A solution of this diacetylenic acid (53 mg.) in ethyl acetate (30 c.c.) was fully hydrogenated, employing Adams's catalyst (20 mg.). After the reaction was completed (hydrogen absorption, 18 c.c. Theory for 2$\equiv$, 17·2 c.c.) the catalyst and solvent were removed, giving a crystalline residue. Crystallisation of this from methanol gave plates, m. p. 66—67° undepressed on admixture with a sample of authentic stearic acid.

Linoleic Acid (VI).—A solution of the diacetylenic acid (V) (563 mg.) in ethyl acetate (40 c.c.) was stirred in an atmosphere of hydrogen in the presence of palladium–calcium carbonate catalyst (100 mg.; 2%) until hydrogen corresponding to the uptake for two double bonds had been absorbed (96 c.c. at 16°/764 mm.). The catalyst was filtered off and the solvent evaporated *in vacuo* at low temperature. The residue consisted of a pale-yellow oil, n_D^{20} 1·4678, which solidified completely on being cooled to −15° (Matthews, Brode, and Brown, *J. Amer. Chem. Soc.*, 1941, **63**, 1064, give m. p. −5°, n_D^{20} 1·4699, for pure linoleic acid). The product was dissolved in light petroleum (b. p. 40—60°; 10 c.c.), transferred to a weighed filter beaker, cooled to 0°, and treated with a solution of bromine in light petroleum until a permanent colour resulted. After 16 hours at 0°, the slightly gummy crystalline precipitate was filtered off, washed with a little ice-cold light petroleum, dried *in vacuo*, and weighed. The weight of bromination product (365 mg.) corresponded to a tetrabromide number of 64·8, thus indicating that the product of partial hydrogenation contained 63% of linoleic acid (Matthews, Brode, and Brown, *loc. cit.*, give 102·9 as the tetrabromide number of pure linoleic acid). Crystallisation of the product from

ethylene dichloride gave plates, m. p. 113—114° undepressed on admixture with authentic 9 : 10 : 12 : 13-tetrabromostearic acid prepared from naturally occurring linoleic acid.

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433. *Alicyclic Glycols. Part IV. Toluene-p-sulphonyl and Methanesulphonyl Derivatives of cycloHexane-1 : 3-diol.*

By M. F. CLARKE and L. N. OWEN.

Mono- and di-toluene-*p*-sulphonyl and -methanesulphonyl derivatives of the *cis*- and the *trans*-form of *cyclo*hexane-1 : 3-diol have been prepared. In reactions with alkali, potassium acetate, sodium benzoate, and lithium chloride, elimination occurs, in some cases exclusively, and unsaturated products are formed. With sodium iodide, replacement more readily takes place, leading to the formation of 1 : 3-di-iodo*cyclo*hexane from the disulphonates.

IN Parts I and II (Clarke and Owen, *J.*, 1949, 315; Owen and Robins, *ibid.*, p. 320) the properties of some derivatives, in particular the sulphonate esters, of *cyclo*hexane-1 : 2- and -1 : 4-diol were considered. This investigation has now been extended to *cyclo*hexane-1 : 3-diol, the chemistry of which has been sporadically studied by earlier workers. Most of these obtained the diol by hydrogenation of resorcinol, generally in poor yield owing to the simultaneous occurrence of hydrogenolysis, which appears to take place particularly readily with 1 : 3-glycols (cf. Connor and Adkins, *J. Amer. Chem. Soc.*, 1932, **54**, 4678). The most extensive investigations were made by Palfray and Sabetay (*Bull. Soc. chim.*, 1928, [iv], **43**, 895), Rothstein, Palfray, and Sontag (*ibid.*, 1929, [iv], **45**, 683; *Compt. rend.*, 1929, **189**, 188), and Rothstein (*Ann. Chim.*, 1930, [x], **14**, 461). Many esters and ethers were prepared; most of these were liquids, but a solid dibenzoate was described, the *cis*- and the *trans*-form of which were separated by fractional crystallisation; these benzoates were very resistant to hydrolysis, but eventually, with some difficulty, the *cis*- and the *trans*-diol were obtained. Lindemann and Baumann (*Annalen*, 1929, **477**, 78) also succeeded in separating the dibenzoates, but failed to effect their hydrolysis; they obtained the *cis*- and the *trans*-diol from the bisphenylurethanes and bistriphenylmethyl ethers. The latter derivatives were also used for this purpose by Coops, Dienske, and Aten (*Rec. Trav. chim.*, 1938, **57**, 303). The most recent work is that of Rigby (*J.*, 1949, 1586, 1588) who separated the stereoisomers by fractional crystallisation from acetone; he also resolved the *trans*-diol, thus providing the first conclusive proof of the stereochemical structures (the failure of Lindemann and Baumann to resolve the *cis*-diol cannot be regarded as satisfactory evidence). It is interesting that these were originally allocated on the basis of the relative melting points of derivatives, on the assumption that *cis*- had melting points lower than *trans*-forms; by chance, this happened to be so for all derivatives described at the time, but, as will be evident in the sequel, this supposition is not always correct.

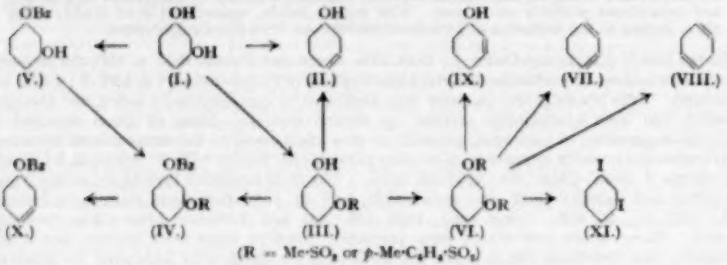
Resorcinol was hydrogenated in methanol over Raney nickel. Hydrogenolysis always occurred, a considerable amount of *cyclo*hexanol being formed, but the *cyclo*hexane-1 : 3-diol (yield, 45%) was readily purified by fractional distillation. Apart from the rather tedious nature of the process, little difficulty was found in the preparation and separation of the *cis*- and the *trans*-dibenzoate. The only previously successful hydrolysis of these esters had been carried out by Rothstein (*loc. cit.*), and we have confirmed his observation that with boiling alcoholic potassium hydroxide a long period of heating is necessary. In the case of *cyclo*hexane-1 : 4-diol, however, it had been found (Owen and Robins, *loc. cit.*) that a particularly satisfactory method for the preparation of the diols from the *cis*- and the *trans*-diacetate was catalytic alcoholysis by a trace of sodium methoxide in cold methanol. This procedure failed completely with the 1 : 3-dibenzoates, thus providing a further illustration of their greater stability, but at 50° alcoholysis proceeded smoothly, and in excellent yields; the ease of isolation by this method is in marked contrast to the drastic and much less efficient hydrolytic process.

Rothstein (*loc. cit.*) made the rather remarkable claim that benzoylation of the pure *cis*-diol is accompanied by partial inversion and gives some *trans*-dibenzoate. No experimental details were given, nor was there any indication of the method of benzoylation which brought about

this change, and it is more probable that his *cis*-diol was impure and contained some of the *trans*-isomer. Lindemann and Baumann (*loc. cit.*), and Rigby (*loc. cit.*), obtained only the *cis*-dibenzoate from the *cis*-diol, and we have confirmed their results.

By dehydration of *cyclo*hexane-1 : 4-diol over alumina, Olberg, Pines, and Ipatieff (*J. Amer. Chem. Soc.*, 1944, **66**, 1096) obtained 1 : 4-epoxy*cyclo*hexane. However, with the 1 : 3-diol (I) no oxide could be detected, the main product being *cyclo*hexen-4-ol (II).

From the appropriate form of the diol, the following new solid derivatives were prepared by standard methods: *cis*-bisphenylurethane, *cis*- and *trans*-dimethanesulphonates, *cis*- and *trans*-ditoluene-*p*-sulphonates. The formation of monoesters took place less readily than in the 1 : 4-series (cf. Owen and Robins, *loc. cit.*). Thus, the 1 : 3-diol reacted only very slowly with 1 mole of toluene-*p*-sulphonyl chloride in pyridine at 0°, and it was necessary to allow the reaction to proceed at room temperature for 3 days in order to obtain the monotoluene-*p*-sulphonate (III). The products from the *cis*- and the *trans*-diol were oils, but on benzoylation gave the crystalline benzoate toluene-*p*-sulphonates (IV). Methanesulphonyl chloride is considerably more reactive than toluene-*p*-sulphonyl chloride, and to avoid excessive formation of the dimethanesulphonates much milder conditions were necessary; these monoesters also were liquids, but on benzoylation gave crystalline benzoate methanesulphonates.



(R = $Me{\cdot}SO_2$ or p-$Me{\cdot}C_6H_4{\cdot}SO_2$)

A mixture of the stereoisomeric monobenzoates was prepared by Rothstein (*loc. cit.*), apparently in poor yield, by treatment of the mixed 1 : 3-diol with 1 mole of benzoyl chloride in the absence of any base. Dimroth and Resin (*Ber.*, 1942, **75**, 322) also prepared some monoesters of the 1 : 3-diol in their search for a route to 3-hydroxy*cyclo*hexanone, but the individual *cis*- and *trans*-monobenzoates were first prepared by Rigby (*loc. cit.*), by partial hydrolysis of the respective dibenzoates. By applying the method used successfully in the 1 : 4-series (Owen and Robins, *loc. cit.*) we have independently obtained the pure *cis*- (yield, 60%) and *trans*-monobenzoates (yield, 42%) (V); both were oils, but were characterised by methanesulphonation and toluene-*p*-sulphonation to give the crystalline derivatives (IV) identical with those obtained by benzoylation of the monomethanesulphonates and monotoluene-*p*-sulphonates. The monobenzoates also gave the crystalline phenylurethanes subsequently described by Rigby, one of which, m. p. 167°, derived from the *cis*-compound, is probably identical with the substance m. p. 168—169°, of hitherto unknown configuration, obtained by Rothstein from his mixed monobenzoate.

The melting points of the new derivatives are recorded in the Table, and it is of interest that in every case where both forms are solid the *cis*-form has the higher value.

Derivatives of cyclo*hexane*-1 : 3-*diol*.

	M. p.			M. p.	
	cis-.	*trans*-.		*cis*-.	*trans*-.
Ditoluene-*p*-sulphonate	108°	92°	Benzoate methanesulphonate ...	104°	65°
Dimethanesulphonate	125	97·5	Benzoate toluene-*p*-sulphonate	97	89
Toluene-*p*-sulphonate methanesulphonate	—	85	Benzoate phenylurethane	167	112
			Bisphenylurethane	—	72—73

In previous papers in this series, attention was drawn to the possibility of the formation of epoxy*cyclo*hexanes by intramolecular loss of a sulphonic acid from a monosulphonyl ester of a diol, and such a reaction was shown to occur with the 1 : 2-, but not with the 1 : 4-diol; the behaviour of the 1 : 3-derivatives was therefore of particular interest. Since the elimination of a sulphonyloxy-group in oxide formation is accompanied by inversion on the carbon atom

carrying that group, the compound most likely to yield the 1 : 3-epoxide on treatment with alkali is the *trans*-monotoluene-*p*-sulphonate (or monomethanesulphonate) (III). This compound, in cold methanol, reacted with 1 mole of sodium methoxide, and sodium toluene-*p*-sulphonate was rapidly formed, but the main product was *cyclo*hexen-4-ol (II); the reaction therefore takes the same course as with the 1 : 4-compound.

The *cis*- and the *trans*-dimethanesulphonate (VI), with hot aqueous alkali, gave a mixture of *cyclo*hexa-1 : 3- (VII) and -1 : 4-diene (VIII) and *cyclo*hexen-3-ol (IX), elimination and replacement reactions having taken place. When the dimethanesulphonates were treated with potassium acetate in boiling ethanol, free acid was liberated, indicating the occurrence of elimination or alcoholysis, and the only recognisable products were *cyclo*hexadienes, there being no evidence for the formation of any diacetate, as had been observed in the 1 : 4-series. Furthermore, the *cis*- and the *trans*-ditoluene-*p*-sulphonate, and the *cis*-dimethanesulphonate, with sodium benzoate in methanol gave only *cyclo*hexadienes and the theoretical amount of benzoic acid.

Several derivatives were treated with lithium chloride in boiling ethanol: in no case was substitution observed, the elimination reaction being dominant. The *trans*-monotoluene-*p*-sulphonate (III) gave *cyclo*hexen-4-ol (II); the *cis*- and the *trans*-benzoate toluene-*p*-sulphonate (IV) gave *cyclo*hexen-4-yl benzoate (X); the *cis*- and the *trans*-ditoluene-*p*-sulphonate and the *trans*-dimethanesulphonate (VI) gave *cyclo*hexadienes. Some substitution, however, occurred with sodium iodide in acetone, and 1 : 3-di-iodo*cyclo*hexane (XI) was obtained from the *trans*-ditoluene-*p*-sulphonate and from the *cis*- and the *trans*-dimethanesulphonate; the product in each case was a liquid, so that no conclusion could be drawn about its stereochemical homogeneity. Substitution also occurred when the *cis*- and the *trans*-benzoate toluene-*p*-sulphonate (IV) reacted with sodium iodide, but the resulting benzoate iodide could not be separated from accompanying unsaturated material. The di-iodide (XI) is possibly the first 1 : 3-dihalogeno-*cyclo*hexane to be described, since, according to Rothstein (*loc. cit.*), attempts to prepare 1 : 3-dichloro- and 1 : 3-dibromo-*cyclo*hexane by reaction of the 1 : 3-diol with the appropriate hydrogen halide have always given 1 : 4-dihalogeno*cyclo*hexanes. It is unlikely that any such rearrangement would occur under the present conditions; furthermore, both stereoisomeric forms of 1 : 4-di-iodo*cyclo*hexane are crystalline solids, whereas the di-iodide now obtained is a liquid.

Considering the results as a whole, it is clear that in the reactions of the sulphonyl esters of *cyclo*hexane-1 : 3-diol elimination takes place even more readily than with derivatives of the 1 : 2- and 1 : 4-diols. This is particularly evident in the reactions with lithium chloride, in which replacement of a sulphonyloxy-group by chlorine occurs readily in the 1 : 2- and the 1 : 4-, but not in the 1 : 3-, series.

The formation of *cyclo*hexen-3-ol (IX) from the dimethanesulphonates (VI) is of interest, since in the other instances when a *cyclo*hexenol was formed it was the isomer (II). At first sight it may appear that (IX) could be formed *via* (II) by isomerisation under the alkaline conditions of the reaction, since it is known that $\beta\gamma$-unsaturated alcohols undergo such changes in the presence of alkali (cf. Hargreaves and Owen, *J.*, 1947, 753, 756). The present conditions, however, are much milder than are usually necessary to bring about the isomerisation, and (II) was in fact unchanged by being heated at 100° with 10% aqueous alkali. The elimination to give (IX) rather than (II) must therefore be a consequence of the presence of the two sulphonyloxy-groups in the molecule.

Experimental.

cis- *and* trans-cyclo*Hexane*-1 : 3-*diol*.—Resorcinol (200 g.) in methanol (200 c.c.) was hydrogenated at 130°/120 atm. over Raney nickel (*ca.* 20 g.), prepared by the method of Pavlic and Adkins (*J. Amer. Chem. Soc.*, 1946, **68**, 1471). The rate of absorption depended on the freshness of the catalyst, but was usually substantially complete after *ca.* 24 hours; with one particularly active batch, most of the absorption had occurred within 10 hours, and prolongation of the reaction then led to almost complete hydrogenolysis. The solution was diluted with more methanol, filtered, and concentrated; fractional distillation then gave a considerable amount of *cyclo*hexanol, b. p. 88°/25 mm. (phenylurethane, m. p. 82°), followed by *cyclo*hexane-1 : 3-diol, b. p. 130—140°/6 mm., n_D^{20} 1·5015, as a viscous oil. There was a small residue (*ca.* 10 g.) of resorcinol. The average yield of diol was 160 g.

The oil (97·5 g.) was dissolved in pyridine (350 g.), and benzoyl chloride (285 g.) was slowly added, with stirring, at 0°. The mixture was left overnight at room temperature, then heated on the steam-bath for an hour, cooled, and diluted with 4*N*-sulphuric acid (2 l.). The precipitated oil was taken up in chloroform, and the extract was washed with dilute sulphuric acid, aqueous potassium carbonate, and finally with water, dried (Na_2SO_4), and evaporated to an oil, which on treatment with ethanol (40 c.c.) partly crystallised. The solid (100 g.) was collected, and on recrystallisation from methanol gave the *trans*-dibenzoate as plates, m. p. 124°. The ethanolic solution was concentrated, treated with a little

light petroleum (b. p. 40—60°), and set aside in the refrigerator; it slowly crystallised, and after trituration with cold methanol the solid was recrystallised from the minimum amount of boiling methanol to give short thick needles of the *cis*-dibenzoate, m. p. 67·5°, depressed to 58° on admixture with the *trans*-isomer.

The *trans*-dibenzoate (50 g.) was dissolved in dry methanol (150 c.c.), and a 5% solution of sodium in dry methanol (0·5 c.c.) was added. The mixture, protected from moisture, was warmed at *ca.* 50° for 24 hours. Water (0·5 c.c.) was then added, and the alkali was neutralised with carbon dioxide. Filtration and removal of methanol by distillation, gave a liquid which on fractionation gave methyl benzoate, b. p. 91°/15 mm., and the *trans*-diol (14 g., 79%), b. p. 140—142°/15 mm.; the latter solidified, and on recrystallisation from ethyl acetate formed plates, m. p. 115·5°. The *bisphenylurethane* of *trans*-*cyclo*hexane-1 : 3-diol crystallised from light petroleum (b. p. 80—100°) in fine needles, m. p. 72—73° (Found: C, 68·0; H, 6·0. $C_{32}H_{32}O_4N_2$ requires C, 67·8; H, 6·3%).

The *cis*-dibenzoate (29 g.) was treated in a similar way. On removal of the methanol, however, the *cis*-diol crystallised from the methyl benzoate solution. Light petroleum (b. p. 40—60°) (150 c.c.) was therefore added, and the diol was filtered off and washed with light petroleum (yield, 9·2 g.). Recrystallisation from acetone gave 8·7 g. (84%), m. p. 85·5°. A portion (1·0 g.) was benzoylated under the conditions used for the mixed diol; recrystallisation of the product from methanol gave 2·5 g. (90%) of *cis*-dibenzoate, m. p. and mixed m. p. 67°, with no indication of any *trans*-isomer.

Dehydration of cyclo*Hexane*-1 : 3-*diol*.—The mixed diol (21 g.) and activated alumina (15 g.) were heated, in an oil-bath at *ca.* 240°, in a flask fitted with a short fractionating column, the distillate being collected during 20 hours. Water (1·8 g.) was separated from the organic layer, and the latter was dried (Na_2SO_4) and distilled to give *cyclo*hexen-4-ol (8·0 g.), b. p. 160—163°, n_D^{20} 1·4810, characterised as the α-naphthylurethane, m. p. 128·5°.

Ditoluene-p-*sulphonates*.—(*a*) The *trans*-diol (6·0 g.), toluene-*p*-sulphonyl chloride (19·6 g.), and pyridine (100 c.c.) were set aside overnight and the solution, containing much pyridine hydrochloride, was then diluted with chloroform (150 c.c.) and washed with 4*N*-sulphuric acid (2 × 200 c.c.), followed by water. The chloroform solution was dried (Na_2SO_4) and evaporated to an oil, which solidified. The trans-*ditoluene*-p-*sulphonate* crystallised from methanol in rectangular plates (18·9 g., 86%), m. p. 90°, raised on further crystallisation to 92° (Found: C, 56·8; H, 5·6. $C_{28}H_{32}O_6S_2$ requires C, 56·6; H, 5·7%).

(*b*) The *cis*-diol (2·0 g.), similarly treated, gave the cis-*ditoluene*-p-*sulphonate* (6·55 g., 88·5%), which crystallised from chloroform–light petroleum (b. p. 80—100°) in plates, m. p. 108°, depressed to 84—85° on admixture with the *trans*-derivative (Found: C, 56·9; H, 6·1%).

Dimethanesulphonates.—(*a*) Methanesulphonyl chloride (9·9 g.) was slowly added to a stirred solution of the *trans*-diol (5·0 g.) in pyridine (50 c.c.) at 0°; the solution was then set aside overnight and worked up as for the ditoluene-*p*-sulphonyl derivative. The trans-*dimethanesulphonate* (11·4 g., 97%) solidified on removal of the chloroform and crystallised from methanol in rosettes of needles, m. p. 97·5° (Found: C, 35·6; H, 5·8. $C_8H_{14}O_6S_2$ requires C, 35·3; H, 5·9%).

(*b*) The *cis*-diol (1·25 g.) similarly gave the cis-*dimethanesulphonate* (2·5 g., 85%), which crystallised from methanol in needles, m. p. 125° (Found: C, 35·3; H, 6·1%). A mixed m. p. with the *trans*-derivative was 86—87°.

It was possible to separate the *cis*- and the *trans*-dimethanesulphonate, prepared from the mixed diol in a similar way, by fractional crystallisation from methanol, the *cis*-compound being the less soluble. Both were soluble in hot water, but only the *trans*-derivative readily crystallised on cooling.

Monobenzoates.—(*a*) Benzoyl chloride (5·8 g.) in pure chloroform (150 c.c.) was added during 4 hours to a stirred solution of the *trans*-diol (4·8 g.) in pyridine (50 c.c.) at −10°. The solution was set aside at room temperature overnight and then washed successively with dilute sulphuric acid and aqueous sodium carbonate, dried (Na_2SO_4), and evaporated to an oil, which deposited some crystalline material. The whole product was dissolved in the minimum amount of boiling methanol; when cooled, the *trans*-dibenzoate (2·2 g.), m. p. 122°, separated and was removed. The methanol solution was then evaporated to an oil, which on distillation gave the *trans*-monobenzoate (3·8 g., 42%), b. p. 120—130° (bath)/0·005 mm., as a viscous oil. A small portion, treated with phenyl isocyanate in the usual way, gave the *trans*-benzoate phenylurethane, which crystallised from benzene–light petroleum (b. p. 60—80°) in rosettes of needles, m. p. 112° (Found: C, 70·9; H, 6·1. Calc. for $C_{20}H_{21}O_4N$: C, 70·8; H, 6·25%). Treatment of another portion with acetyl chloride in pyridine gave the trans-*acetate benzoate* as an oil, b. p. 85—90°/0·0004 mm. (Found: C, 68·9; H, 7·2. $C_{15}H_{18}O_4$ requires C, 68·7; H, 6·9%).

(*b*) The *cis*-diol, on benzoylation under similar conditions, gave the *cis*-monobenzoate (60%), b. p. 130—135° (bath)/0·003 mm. It gave a phenylurethane, m. p. 167°.

Benzoate Toluene-p-*sulphonates*.—The *trans*-monobenzoate (3·8 g.) was treated overnight with toluene-*p*-sulphonyl chloride (3·3 g.) in pyridine (30 c.c.) and worked up in chloroform (60 c.c.) as previously described. The trans-*benzoate toluene*-p-*sulphonate* (4·65 g., 72%) crystallised from light petroleum (b. p. 80—100°) in plates, m. p. 89° (Found: C, 64·4; H, 6·1. $C_{20}H_{20}O_5S$ requires C, 64·2; H, 5·9%). Similar treatment of the *cis*-monobenzoate (2·0 g.) gave the cis-*benzoate toluene*-p-*sulphonate* (2·8 g., 82·5%), which crystallised from methanol in fine needles, m. p. 97° (Found: C, 63·7; H, 5·7%). On admixture of this with the *trans*-compound the m. p. was depressed to 78—80°.

Benzoate Methanesulphonates.—These were prepared in a similar way to the preceding compounds. The trans-*benzoate methanesulphonate* (83%) formed needles, m. p. 65°, from light petroleum (b. p. 80—100°) (Found: C, 56·4; H, 6·0. $C_{14}H_{18}O_5S$ requires C, 56·4; H, 6·1%). The cis-*benzoate methanesulphonate* (92%) crystallised from light petroleum (b. p. 80—100°) in needles, m. p. 104° (Found: C, 56·7; H, 6·6%).

Monotoluene-p-sulphonates.—A solution of toluene-*p*-sulphonyl chloride (24·6 g.) in pyridine (60 c.c.) was added during 5 hours to a stirred solution of the *trans*-diol (17·4 g.); the mixture was then set aside for 3 days. Chloroform (250 c.c.) was then added, and after the pyridine had been washed out as previously described the dried solution was evaporated to an oil. This was dissolved in light petroleum (b. p. 60—80°) containing a few drops of chloroform, and seeded with the *trans*-ditoluene-*p*-sulphonate, whereupon a small amount of this substance crystallised and was removed. Evaporation then gave the trans-*monotoluene*-p-*sulphonate* as an oil (25 g.) which was clarified by dissolution in chloroform, shaking with charcoal, filtration, and evaporation to an almost colourless viscous liquid (Found: S, 10·5. $C_{13}H_{18}O_4S$ requires S, 11·85%). The *cis*-monotoluene-*p*-sulphonate, similarly prepared, was also an oil.

Treatment of these derivatives with benzoyl chloride in pyridine gave the corresponding benzoate toluene-*p*-sulphonate, *cis*-, m. p. 97°, and *trans*-, m. p. 89°, identical with those described above.

Monomethanesulphonates.—A solution of methanesulphonyl chloride (1 g.) in pure chloroform (80 c.c.) was added during 3 hours to a stirred solution of the *trans*-diol (1·0 g.) in pyridine (20 c.c.) at −20°. The solution was set aside at room temperature overnight and then stirred with sodium hydrogen carbonate (1 g.) and a few drops of water until neutral. The solution was then shaken with anhydrous sodium sulphate, filtered, and evaporated to an oil, which was dissolved in the minimum amount of boiling methanol. On cooling, some *trans*-dimethanesulphonate (0·37 g., m. p. 97°) crystallised and was removed. Evaporation of the solution then gave the crude *trans*-monomethanesulphonate as a viscous water-soluble oil, which could not be distilled without decomposition. The *cis*-monomethanesulphonate had similar properties.

Treatment of these derivatives with benzoyl chloride in pyridine gave the *trans*-, m. p. 64°, and the *cis*-form, m. p. 103°, respectively of the benzoate methanesulphonate, identical with those previously described.

The *trans*-monomethanesulphonate (0·4 g.) with toluene-*p*-sulphonyl chloride (0·4 g.) in pyridine gave the trans-*methanesulphonate toluene*-p-*sulphonate*, which crystallised from ethanol in laths, m. p. 85° (Found: C, 48·1; H, 6·0. $C_{14}H_{20}O_5S_2$ requires C, 48·3; H, 5·8%). The *cis*-monomethanesulphonate on similar treatment gave an oil.

Reaction of the trans-*Monotoluene*-p-*sulphonate with Sodium Methoxide.*—A 5% solution of sodium in methanol (25 c.c.) was added to the derivative (14·8 g.) in methanol (50 c.c.). Sodium toluene-*p*-sulphonate began to separate after a few minutes. After the mixture had been left for 2 days at room temperature, a few drops of water were added and the residual alkali was neutralised with carbon dioxide. The solution was filtered, and the methanol was removed by distillation through a short fractionating column; the distillate was unsaturated. Distillation of the residue gave a main fraction (4·1 g.), b. p. 94—115°/70 mm., which on redistillation gave *cyclo*hexen-4-ol, b. p. 160—165°, n_D^{20} 1·4806, characterised as the α-naphthylurethane, m. p. 128°.

Reaction of the Dimethanesulphonates with Alkali.—The *cis*-derivative (10 g.) was stirred for 2½ hours at 90° with 5% aqueous sodium hydroxide (120 c.c.), in which it was appreciably soluble. A slow stream of nitrogen was passed through the flask and reflux condenser, and thence, through a calcium chloride tube, to a solution of bromine in carbon tetrachloride. From the latter solution there was obtained the tetrabromide of *cyclo*hexa-1 : 4-diene, m. p. 188°. The alkaline solution was extracted with ether (4 × 50 c.c.), the extracts were dried (Na_2SO_4) and evaporated, and the residual unsaturated oil (3 g.) was distilled to give *cyclo*hexen-3-ol (75%), b. p. 160—165°, n_D^{20} 1·4777, characterised as the phenylurethane, m. p. 107°, and the α-naphthylurethane, m. p. 155° (Willstätter and Sonnenfeld, *Ber.*, 1913, **46**, 2952, give 107° and 156°).

The *trans*-dimethanesulphonate (10 g.) on similar treatment gave 1·0 g. (28%) of *cyclo*hexen-3-ol. For half of the reaction period the stream of nitrogen was passed through pure ethanol, spectroscopic examination of which then showed the presence of *cyclo*hexa-1 : 3-diene (light absorption max., 2580 A.); in addition, the tetrabromide, m. p. 188°, of *cyclo*hexa-1 : 4-diene was obtained as before. In view of the much smaller yield of *cyclo*hexen-3-ol, the aqueous residues were examined for *cyclo*hexane-1 : 3-diol, but none was detected.

After a similar experiment, the *trans*-ditoluene-*p*-sulphonate was recovered quantitatively. The non-reactivity is probably due to its insolubility in aqueous alkali.

Reaction of the Dimethanesulphonates with Potassium Acetate.—A solution of the *trans*-derivative (2·2 g.) and anhydrous potassium acetate (3·9 g.) in ethanol (60 c.c.) was heated under reflux for 24 hours. A bromine absorption train was used, as previously described, and from it the tetrabromide, m. p. 188°, was recovered. The alcoholic solution (which now contained free acetic acid) was diluted with water and neutralised by titration with 0·216N-sodium hydroxide (42·6 c.c., corresponding to the formation of 1·2 moles of acid). Most of the alcohol was then distilled off, and the residual aqueous solution was extracted with chloroform; only unchanged *trans*-dimethanesulphonate (0·7 g.), m. p. 95°, was obtained.

Similar results were obtained with the *cis*-dimethanesulphonate, which was heated for 40 hours; 1·5 moles of acetic acid were liberated, and the tetrabromide, m. p. 188°, was isolated as before.

Reaction of the Disulphonates with Sodium Benzoate.—The *cis*-dimethanesulphonate (1·0 g.) and sodium benzoate (2·7 g.) were heated under reflux in methanol (60 c.c.) for 50 hours. Tetrabromo*cyclo*hexane, m. p. 187°, was obtained, as previously described, from a bromine absorption train. The solution was diluted with water, concentrated to remove methanol, and extracted with ether to yield benzoic acid (0·9 g., 2 moles), m. p. 120°.

Essentially the same results were obtained with the *cis*- and the *trans*-ditoluene-*p*-sulphonate.

Reactions with Lithium Chloride.—(*a*) The *trans*-monotoluene-*p*-sulphonate (4·0 g.) and lithium chloride (2·0 g.) were heated under reflux in ethanol (65 c.c.) for 40 hours. The solvent was then distilled off through a fractionating column (the distillate was unsaturated), and the semi-solid residue was

diluted with water (20 c.c.) and extracted with ether (3 × 40 c.c.). The dried (Na_2SO_4) extracts were evaporated to an oil (1·7 g.), which contained combined sulphur but no halogen; on distillation, some *cyclo*hexen-4-ol (0·71 g., 49%), b. p. 95—102°/80 mm., was obtained before the residue, which probably contained some unchanged toluene-*p*-sulphonate, decomposed. The *cyclo*hexenol was identified by formation of the α-naphthylurethane, m. p. 128°.

(*b*) A solution of the *trans*-benzoate toluene-*p*-sulphonate (1·0 g.) and lithium chloride (0·35 g.) in ethanol (25 c.c.) was heated under reflux for 40 hours and then concentrated to small bulk. The residue was diluted with water and extracted with chloroform, to give an unsaturated oil (0·53 g.), b. p. 80° (bath)/0·001 mm., n_D^{20} 1·5218, which contained no halogen. It was hydrolysed by being heated with 10% aqueous potassium hydroxide for 4 hours on the steam-bath, and gave *cyclo*hexen-4-ol, characterised as the 3 : 5-dinitrobenzoate, m. p. and mixed m. p. 100—101°.

Similar results were obtained with the *cis*-benzoate toluene-*p*-sulphonate.

(*c*) The *trans*-ditoluene-*p*-sulphonate (1·0 g.) and lithium chloride (0·5 g.) were heated under reflux in ethanol (35 c.c.) for 24 hours, a stream of nitrogen being passed through the apparatus and into a solution of bromine in carbon tetrachloride. From the latter, there were obtained needles of tetrabromo-*cyclo*hexane (0·25 g., corresponding to a 30% yield of *cyclo*hexa-1 : 4-diene), m. p. 180°, raised on recrystallisation from acetone to m. p. 188°. The alcohol was distilled off, and the residue was dissolved in water (40 c.c.); extraction with ether (3 × 70 c.c.) gave no product.

No chlorine-containing product was obtained on repetition of the experiment (i) with a period of heating of only 3 hours, when 65% of the ditoluene-*p*-sulphonate was recovered unchanged; (ii) when the reaction was carried out in a sealed tube at 150° for 2 hours, or (iii) under the original conditions, with either the *cis*-ditoluene-*p*-sulphonate or the *trans*-dimethanesulphonate.

Reactions with Sodium Iodide.—(*a*) The *cis*-ditoluene-*p*-sulphonate (1·0 g.), sodium iodide (1·8 g.), and pure acetone (25 c.c.) were heated in a sealed tube for 1 hour at 100°. The dark brown solution was filtered from sodium toluene-*p*-sulphonate (0·73 g., 80%) and was concentrated to a semi-solid residue; this was diluted with water (25 c.c.) and extracted with ether (3 × 35 c.c.). The extracts were washed with aqueous sodium thiosulphate to remove free iodine, dried (Na_2SO_4), and evaporated below 40° under reduced pressure to give a colourless oil. Distillation at 65° (bath)/0·0001 mm., gave 1 : 3-*di-iodocyclo*hexane (0·37 g., 47%), n_D^{20} 1·6225 (Found: I, 76·5. $C_6H_{10}I_2$ requires I, 75·6%).

A compound with similar properties was obtained (i) from the *cis*-dimethanesulphonate by heating it with sodium iodide in acetone under reflux for 100 hours, and (ii) from the *trans*-ditoluene-*p*-sulphonate by heating under reflux for 20 hours or at 100° for 2 hours.

(*b*) The *trans*-benzoate toluene-*p*-sulphonate (1·5 g.), sodium iodide (1·5 g.) and acetone (40 c.c.) were heated in a sealed tube for 3 hours at 100°. Sodium toluene-*p*-sulphonate (0·66 g., 84%) was removed, and the acetone solution was worked up as before to give an almost colourless oil (1·2 g.). Unchanged starting material (0·15 g.) was separated from this by crystallisation from aqueous methanol, and the recovered oil was distilled at 80° (bath)/0·0004 mm. to give a colourless liquid (1·0 g.), n_D^{20} 1·5514, which contained iodine (Found: I, 16·9%) but no sulphur. It was, however, unsaturated and could not be further purified. Similar results were obtained with the *cis*-derivative.

Stability of cycloHexen-4-ol.—Prepared by dehydration of *cyclo*hexane-1 : 4-diol with sulphuric acid (cf. Senderens, *Compt. rend.*, 1925, **180**, 191), *cyclo*hexen-4-ol had b. p. 162—163°, n_D^{20} 1·4860, and gave the phenylurethane, m. p. 81°. A portion of the alcohol (1·3 g.) was stirred under reflux with 10% aqueous sodium hydroxide (20 c.c.) at 100° for 5 hours. Light petroleum (b. p. 40—60°) was then added, and the organic layer was removed, dried ($CaCl_2$), and evaporated to an oil, which on distillation gave only *cyclo*hexen-4-ol (0·85 g.), b. p. 162—164°, n_D^{20} 1·4852, characterised as the phenylurethane, m. p. and mixed m. p. 81°. (The phenylurethane of *cyclo*hexen-3-ol has m. p. 107°.)

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434. *Alicyclic Glycols. Part V.* 3-*Hydroxymethyl*cyclo*hexanol.*

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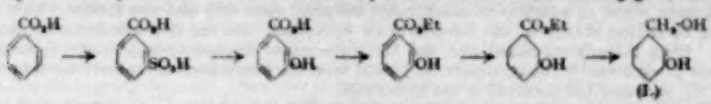
The synthesis of 3-hydroxymethyl-*cyclo*hexanol (I) from *m*-hydroxybenzoic acid is described. Several derivatives of the *cis*- and the *trans*-form have been obtained and their reactions studied. Toluene-*p*-sulphonyl and methanesulphonyl substituted into the primary hydroxyl group undergo normal replacement by alkoxy-, acetoxy-, chloro-, and iodo-groups; sulphonate esters of the secondary group more readily undergo the elimination reaction, but substitution, when it occurs, is accompanied by inversion of configuration. The cyclic ether, 1 : 3-*endo*methyleneoxy-*cyclo*hexane (XII) has been obtained by the action of alkali on the primary monotoluene-*p*-sulphonate and on the primary monochloride (3-chloromethyl-*cyclo*hexanol).

The synthesis and properties of 4-hydroxymethyl-*cyclo*hexanol were recorded in Part III (Owen and Robins, *J.*, 1949, 326). The synthesis of 3-hydroxymethyl-*cyclo*hexanol (I) has now been accomplished by a similar series of reactions. Benzoic acid was converted in 90% yield

into *m*-hydroxybenzoic acid by sulphonation, and fusion of the sodium benzene-*m*-sulphonate with potassium hydroxide, the use of sodium hydroxide for the fusion having given unsatis-



(I.)

factory results (cf. Offermann, *Annalen*, **1894**, **280**, 5). An alternative route to the *m*-hydroxy-acid, involving diazotisation of *m*-aminobenzoic acid, was also investigated, but the overall yield was small. Esterification, followed by hydrogenation over Raney nickel, gave ethyl 3-hydroxy*cyclo*hexanecarboxylate in good yield; this compound had previously been obtained, in very poor yield, from 3-amino*cyclo*hexanecarboxylic acid by Bauer and Einhorn (*ibid.*, **1901**, **319**, 324). Bouveault–Blanc reduction then gave the diol (I) as a viscous liquid from which, unlike the 4-hydroxymethyl isomer, no solid form could be separated. The overall yield of diol, from benzoic acid, was nearly 50%.

As a by-product from the Bouveault–Blanc reduction, a small amount of 3-hydroxy*cyclo*hexanecarboxylic acid was recovered, which after purification was the *cis*-form, m. p. 132° (cf. Einhorn and Coblitz, *ibid.*, **1896**, **291**, 297; Perkin and Tattersall, *J.*, 1907, **91**, 480). This was esterified, and then reduced by the Bouveault–Blanc method, but again, as shown by the preparation of derivatives (see below), the resulting diol was a mixture of stereoisomers; not unexpectedly, therefore, some isomerisation had occurred during the reduction. The mixed diol was also prepared by reduction of the hexahydro-ester with lithium aluminium hydride (cf. Nystrom and Brown, *J. Amer. Chem. Soc.*, **1947**, **69**, 1197, 2548).

Since the diol itself could not be obtained directly in any one pure stereochemical form, attention was directed towards the preparation of suitable derivatives. In this way it was eventually possible to achieve the desired separation, and also, on the basis of certain reactions, to allocate the appropriate stereochemical structures to the derivatives.

The diacetate and dibenzoate were liquids, but the di-*p*-nitrobenzoate, dimethanesulphonate and bisphenylurethane were solids, each of which by fractional crystallisation was separated into two forms, m. p.s 141° and 162°; 103·5° and 103°; 162° and 122°, respectively. The bis-3 : 5-dinitrobenzoate, m. p. 181°, and ditoluene-*p*-sulphonate, m. p. 95°, were also solids, but only the one form of each could be crystallised. By distillation of one of the bisphenylurethanes (m. p. 162°) with sodium hydroxide, the corresponding form of the diol was obtained as a liquid; from this, a bis-3 : 5-dinitrobenzoate, m. p. 181°, a dimethanesulphonate, m. p. 103·5°, and a ditoluene-*p*-sulphonate, m. p. 95°, were prepared, each of which was identical with the derivative of similar melting point obtained from the mixed diol. Furthermore, hydrolysis of the di-*p*-nitrobenzoate, m. p. 141°, also gave the same stereoisomer of the diol, as shown by formation of the dimethanesulphonate, m. p. 103·5°. (The similar melting points of the two stereoisomeric dimethanesulphonates did not introduce any uncertainty, since a mixture of the two had m. p. *ca.* 86°; either form could therefore be readily recognised.) This diol also gave a bis-α-naphthylurethane, m. p. 166·5°. Hydrolysis of the di-*p*-nitrobenzoate, m. p. 162°, gave the other form of the diol, from which the different dimethanesulphonate, m. p. 103°, was obtained, thus providing additional confirmation of the inter-relationships.

Six derivatives were therefore known of one form, and three of the other form, of the diol; these are summarised in the Table, the stereochemical structures recorded being those assigned later.

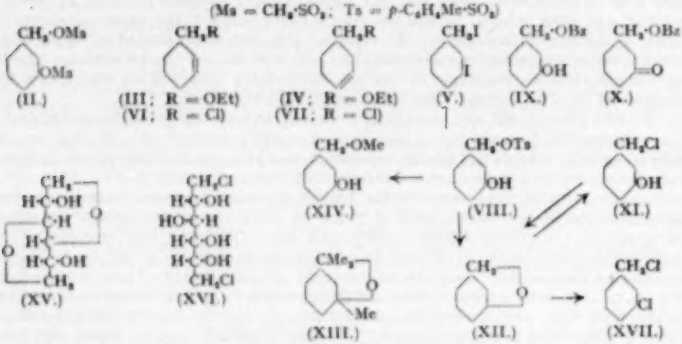
Derivatives of 3-*hydroxymethyl*cyclo*hexanol.*

	M. p.			M. p.	
	cis.	*trans*.		*cis*.	*trans*.
Di-*p*-nitrobenzoate	141°	162°	Ditoluene-*p*-sulphonate	95°	—
Bis-3 : 5-dinitrobenzoate	181	—	Bisphenylurethane	162	122°
Dimethanesulphonate	103·5	103	Bis-α-naphthylurethane	166·5	—

The reactivities of the sulphonyloxy-groups in the methanesulphonyl and toluene-*p*-sulphonyl derivatives were then examined. The *cis*-dimethanesulphonate (II) reacted rapidly and completely when heated with ethanolic potassium hydroxide, and gave an ethoxymethyl-*cyclo*hexene (III) or (IV) as the main product; the primary group thus underwent solvolysis, whilst the secondary group was lost by elimination. With aqueous alkali, however, although some hydroxymethyl*cyclo*hexene was probably formed, a small amount of the free *trans*-diol was obtained, identified as the di-*p*-nitrobenzoate; under these conditions, therefore, the

secondary group to some extent undergoes replacement with inversion. Somewhat similar results were obtained by treatment with aqueous alkali of the (*cis* + *trans*)-ditoluene-*p*-sulphonate, when, in addition to unsaturated material, some free diol was formed which was shown to consist mainly of the *trans*-form by conversion into the di-*p*-nitrobenzoate, m. p. 161°. Since the original mixed diol, and hence the mixed ditoluene-*p*-sulphonate, appears to contain predominantly the *cis*-isomer (as judged from the proportions of *cis*-derivatives formed from it), inversion has occurred in the hydrolysis.

When the *cis*-dimethanesulphonate was treated with potassium acetate in boiling ethanol, the solution became acid to an extent corresponding to the formation of 0·9 mole of methanesulphonic acid. The main product isolated was ethoxymethyl*cyclo*hexene (III) or (IV), but some *trans*-diacetate was also formed, characterised by hydrolysis to *trans*-diol and formation of the di-*p*-nitrobenzoate. The *trans*-dimethanesulphonate, on similar treatment, gave ethoxymethyl*cyclo*hexene and the *cis*-diacetate. Thus, although the possible products were not all isolated and may not all have been formed, it is clear that the primary sulphonyloxy-group undergoes replacement both by the acetoxy- and by the ethoxy-group, whilst the secondary sulphonyloxy-residue undergoes both elimination and replacement (the latter with inversion).



The *cis*-dimethanesulphonate reacted readily with sodium iodide in acetone to give 3-iodomethyl*cyclo*hexyl iodide (V), but with lithium chloride in ethanol a high yield of the elimination product, chloromethyl*cyclo*hexene (VI) or (VII), was obtained. The behaviour of the secondary group towards these two reagents is similar to that observed with methanesulphonates of *cyclo*hexane-1 : 3-diol (Part IV, preceding paper).

Mono-esters of 3-hydroxymethyl*cyclo*hexanol were prepared by methods similar to those used for the 4-hydroxymethyl isomer (Owen and Robins, *loc. cit.*). The ω-toluene-*p*-sulphonate (VIII) and the ω-benzoate (IX) were liquids; the latter derivative on oxidation with chromic acid gave 3-benzoyloxymethyl*cyclo*hexanone (X). The ω-methanesulphonate was a water-soluble oil which could not be satisfactorily purified. When the *cis*-diol was heated with fuming hydrochloric acid, *cis*-3-chloromethyl*cyclo*hexanol (XI) was formed, which gave an α-naphthylurethane, m. p. 142°; the reaction was slower than had been observed in the preparation of 4-chloromethyl*cyclo*hexanol. The chloride was also prepared, as a *cis–trans*-mixture, from the mixed diol; only the *cis*-α-naphthylurethane, m. p. 142°, could be isolated in a pure state from this chloride, although indications of another solid isomer were observed. It was also possible to obtain the chloride by reaction of the ω-toluene-*p*-sulphonate (VIII) with lithium chloride.

The possibility of preparing cyclic oxides by intramolecular elimination of a sulphonic acid between a sulphonyloxy-group and a suitably disposed hydroxyl group has been discussed in earlier papers in this series, but only in the case of 1 : 2-epoxy*cyclo*hexane has the method been successful. During the present work, in one preparation of the monotoluene-*p*-sulphonate (VIII) an odour suggestive of a cyclic oxide was observed, and it was found that when (VIII) was heated with solid or aqueous sodium hydroxide a small yield of a volatile crystalline compound, $C_7H_{12}O$, m. p. 96—97°, was obtained. This material, which has a pronounced camphor-

aceous odour, is the hitherto unknown 1 : 3-*endo*methyleneoxy*cyclo*hexane (XII), the simplest analogue of *m*-cineole (XIII). In this reaction, which was carried out on the mixed stereoisomers of (VIII), unsaturated by-products were formed, but a proportion of the monotoluene-*p*-sulphonate was recovered from the reaction mixture; the recovered ester was largely unaffected by further treatment with alkali and was possibly the *trans*-form, since only the *cis*-compound would be expected to give the oxide (inversion accompanying removal of the primary sulphonyloxy-group does not affect the stereochemistry of the ring system). The oxide was also formed when (VIII) was treated with methanolic sodium hydroxide, but the main product then was 3-methoxymethyl*cyclo*hexanol (XIV), intermolecular reaction with the solvent evidently occurring more readily than intramolecular reaction with the secondary hydroxyl group. The possibility that (XIV) was formed *via* the oxide is very unlikely in view of the stability of the latter (see below).

A more convenient method of preparing the oxide was to treat the chloride (XI) with solid sodium hydroxide, and, since the oxide could be obtained in this way from the chloride derived, as mentioned above, from one stereoisomer of the diol, it follows that this stereoisomer is probably the *cis*-form, since the dehydrochlorination would not be expected to cause any inversion on the carbon atom carrying the hydroxyl group. It is on this evidence, supported by a further observation considered below, that the configurations, already assumed, have been based.

The oxide ring in (XII) is of the type encountered in tetrahydrofuran and in the 3 : 6-anhydrosugars, and in common with such compounds it shows considerable stability. The oxide was unaffected by water at 100°, even in the presence of perchloric acid, or by methanesulphonic or toluene-*p*-sulphonic acid in ether or boiling benzene. Montgomery and Wiggins (*J.*, 1946, 392) found that, when 1 : 4-3 : 6-dianhydrosorbitol (XV), which possesses two such ring systems and is also very stable, is heated with fuming hydrochloric acid, it undergoes ring fission in a direction such that the 1 : 6-dichloro-compound (XVI) is obtained. When the oxide (XII) was similarly treated it gave, according to the amount of hydrochloric acid used, either 3-chloromethyl*cyclo*hexanol (XI) or 3-chloromethyl*cyclo*hexyl chloride (XVII). The ring-opening to give the former compound would not be expected to lead to inversion, and consequently the monochloride formed in this reaction is probably the *cis*-form; it gave an α-naphthylurethane, m. p. 142°, identical with that described above, which, on evidence of oxide-formation, had already been allotted a *cis*-configuration.

Experimental.

m-Hydroxybenzoic Acid.—Sodium hydrogen *m*-sulphobenzoate (239 g.), prepared by the method of Offermann (*loc. cit.*), was mixed to a paste with 45% aqueous sodium hydroxide (95 c.c.) contained in a basin heated on the steam-bath, and powdered sodium hydroxide (48 g.) was then stirred into the mixture, which solidified when allowed to cool. The product was broken into small pieces and added during ½ hour to fused potassium hydroxide (335 g.) contained in an iron vessel, the internal temperature being maintained at 210—220° during the addition and for a further 2½ hours. The cooled mass was then dissolved in water (1 l.), and the solution filtered and acidified with hydrochloric acid. *m*-Hydroxybenzoic acid (133 g., 91%), m. p. 198—200°, was precipitated. It was collected and washed with a little cold water. The use of sodium hydroxide for the fusion gave only a 17% yield.

Ethyl m-Hydroxybenzoate.—Esterification of the acid (126 g.) with ethanol (150 c.c.) and sulphuric acid (24 c.c.) under reflux for 6 hours, followed by dilution with water, gave the ester as a solid (118 g., 89%). After recrystallisation from light petroleum (b. p. 80—100°) it had m. p. 72°.

Ethyl 3-Hydroxycyclohexanecarboxylate.—A solution of ethyl *m*-hydroxybenzoate (145 g.) in ethanol (400 c.c.) was stirred in the presence of Raney nickel (*ca.* 15 g.) with hydrogen at 140°/130 atm. Absorption ceased after 30 hours, and the filtered solution was concentrated and fractionally distilled. Ethyl hexahydrobenzoate (18·5 g.) was collected at 84—90°/16 mm., n_D^{20} 1·4500, followed by ethyl 3-hydroxy*cyclo*hexanecarboxylate (105 g., 70%), b. p. 117—122°/1 mm., n_D^{20} 1·4651. There was a small residue (17·5 g.) of ethyl *m*-hydroxybenzoate.

3-Hydroxymethylcyclohexanol.—(i) Ethyl 3-hydroxy*cyclo*hexanecarboxylate (105 g.) was dissolved in dry ethanol (800 c.c.) contained in a 3-l. flask fitted with a large and efficient reflux condenser. Sodium (85 g.) was added in one portion and the reduction was allowed to proceed as vigorously as possible, the flask being heated on the steam-bath when the initial violence had subsided. When all the sodium had disappeared (6 hours), water (150 c.c.) was added and the alcohol was removed by distillation under reduced pressure. The semi-solid residue was dissolved in a further portion of water (250 c.c.) and continuously extracted with ether for 48 hours. Removal of solvent from the dried (Na_2SO_4) extract gave an oil, which on distillation gave a main fraction (67·0 g., 84%) of *3-hydroxymethylcyclohexanol*, b. p. 117—122°/0·5 mm., 165—166°/27 mm., n_D^{20} 1·4900 (Found: C, 64·3; H, 10·7. $C_7H_{14}O_2$ requires C, 64·6; H, 10·85%). Acidification of the remaining alkaline solution, and extraction with ether, gave a solid acid, m. p. 125°. Repeated recrystallisation from ethyl acetate gave *cis*-3-hydroxy*cyclo*hexanecarboxylic acid (7·5 g.), m. p. 131—132°.

(ii) The recovered *cis*-acid was converted into the ethyl ester, which was then reduced under the conditions described above. The glycol so obtained, b. p. 115—119°/0·5 mm., was shown to be a mixture of stereoisomers by formation of the two di-*p*-nitrobenzoates (see below).

(iii) To a solution of lithium aluminium hydride (0·2 g.) in dry ether (10 c.c.), ethyl 3-hydroxy*cyclo*hexanecarboxylate (2·0 g.) in dry ether (3 c.c.) was added, and the mixture was stirred for 40 minutes. Water (10 c.c.) was then added, followed by 10% sulphuric acid (12 c.c.), and the aqueous layer was removed, washed once with ether to remove unchanged ester, and then continuously extracted with ether. The latter extracts gave the glycol (0·78 g., 52%), b. p. 120—122°/0·5 mm., which was characterised by formation of the two dimethanesulphonyl derivatives (see below).

Diacetate. Acetyl chloride (0·73 g.) was added to a solution of 3-hydroxymethyl*cyclo*hexanol (0·5 g.) in pyridine (5 c.c.), and the mixture was set aside for a few hours. Chloroform was then added, and the solution was washed with dilute hydrochloric acid and with water, dried (Na_2SO_4), and evaporated. Distillation of the residual oil gave the *diacetate* as a mobile liquid (0·7 g.), b. p. 60—70°/0·005 mm., n_D^{25} 1·4511 (Found: C, 62·1; H, 8·7. $C_{11}H_{18}O_4$ requires C, 61·7; H, 8·5%).

Dibenzoate. Prepared in a similar way, this was an oil, which decomposed on attempted distillation.

Di-p-nitrobenzoate. The diol (0·6 g.) in pyridine (150 c.c.) was treated with *p*-nitrobenzoyl chloride (1·5 g.) at 60° for 8 hours, followed by 4 days at room temperature. It was then worked up, as previously described for the diacetate, in chloroform (200 c.c.), and gave an oil (1·5 g.) which solidified when triturated with methanol. Recrystallisation from dioxan (30 c.c.) gave two crops of crystals (0·1 g.), m. p. 137—140°, which when recrystallised from methanol gave the *cis-di-p-nitrobenzoate* as needles, m. p. 141° (Found: N, 6·2. $C_{21}H_{20}O_8N_2$ requires N, 6·5%). Progressive dilution of the dioxan mother-liquors with methanol gave first a small crop of the same material, followed by a new compound, m. p. 155—156°; recrystallisation of the latter from ethanol gave the *trans-di-p-nitrobenzoate* as prisms, m. p. 162° (Found: N, 6·2%). A mixture of the two forms had m. p. 128°.

Bis-3 : 5-dinitrobenzoate. The diol (0·4 g.) in pyridine (10 c.c.) was treated with 3 : 5-dinitrobenzoyl chloride (1·4 g.) under the same conditions as for the *p*-nitrobenzoate. The product (1·3 g., 83%) was crystallised from dioxan to give the *cis-bis-3 : 5-dinitrobenzoate*, which after recrystallisation from ethanol formed needles (0·6 g.), m. p. 181° (Found: C, 48·25; H, 3·4. $C_{21}H_{18}O_{12}N_4$ requires C, 48·65; H, 3·5%). The only other crystalline product obtained on dilution of the dioxan mother-liquor with methanol was the *trans-3 : 5-dinitrobenzoate*, which crystallised from ethanol in needles, m. p. 160° (Found: N, 8·6. $C_{21}H_{14}O_{12}N_4$ requires N, 8·6%).

Dicinnamate. Treatment of the diol with cinnamoyl chloride in pyridine gave a solid product from which only one stereoisomer of the *dicinnamate* could be isolated; it formed rosettes of needles, m. p. 106°, from ethanol (Found: C, 76·5; H, 6·7. $C_{25}H_{24}O_4$ requires C, 76·8; H, 6·7%).

Bisphenylurethane. The diol (1·2 g.) was heated at 80° for 2 hours with phenyl isocyanate (2·9 g.) in a sealed tube. The resulting white solid was crystallised from *ca.* 150 c.c. of 1 : 1 benzene–light petroleum (b. p. 60—80°) and gave 1·95 g. (58%) of the *cis-bisphenylurethane* as needles, m. p. 162° (Found: C, 68·6; H, 6·3. $C_{21}H_{24}O_4N_2$ requires C, 68·5; H, 6·6%). Removal of solvent from the mother-liquors gave a sticky solid, which after several recrystallisations from benzene–light petroleum gave the *trans-bisphenylurethane*, m. p. 122° (Found: N, 7·65. $C_{21}H_{24}O_4N_2$ requires N, 7·6%). A mixture of the two forms had m. p. 120—122°.

Dimethanesulphonate. A solution of methanesulphonyl chloride (2·2 g.) and the diol (1·2 g.) in pyridine (80 c.c.) was left at 0° overnight and then worked up in the usual way with chloroform (150 c.c.). The product (2·6 g.) solidified and was crystallised from ethyl acetate. Two more recrystallisations from this solvent, followed by several from ethanol, gave the *cis-dimethanesulphonate* (1·6 g., 61%) as rosettes of needles (from ethyl acetate), m. p. 103·5° (Found: C, 38·0; H, 6·2. $C_8H_{16}O_6S_2$ requires C, 37·8; H, 6·3%). Concentration of the original ethyl acetate mother-liquor gave a crop of crystals, m. p. *ca.* 90°, which after several recrystallisations from methanol gave the *trans-dimethanesulphonate* (3·8 g., 14·5%), m. p. 103° (Found: C, 38·1; H, 6·5%). A mixture of the two forms had m. p. 86—87°.

Ditoluene-p-sulphonate. The diol (3·8 g.) and toluene-*p*-sulphonyl chloride (11·2 g.) in pyridine, under the conditions described for the methanesulphonate, gave a viscous oil which was taken up in a small quantity of methanol. Crystals slowly separated out, and recrystallisation from methanol gave the *cis-ditoluene-p-sulphonate* as needles, m. p. 95° (Found: C, 57·4; H, 6·1. $C_{21}H_{24}O_6S_2$ requires C, 57·5; H, 6·0%). No other crystalline material could be isolated.

ω-Benzoate. Benzoyl chloride (2·2 g.) in pure chloroform (70 c.c.) was slowly added with good stirring to the diol (2·0 g.) in pyridine (15 c.c.) at −10°. The solution was set aside at room temperature for 2 days and then heated on the steam-bath for 1 hour. The product, isolated as above, was an oil, distillation of which gave the *ω-benzoate* as a viscous liquid (2·3 g.), b. p. 100° (bath)/0·0006 mm., n_D^{25} 1·5287 (Found: C, 71·7; H, 7·9. $C_{14}H_{18}O_3$ requires C, 71·8; H, 7·8%), which failed to give a crystalline methanesulphonate.

ω-Toluene-p-sulphonate. Toluene-*p*-sulphonyl chloride (14·3 g.) in pyridine (20 c.c.) was added during 20 minutes to a stirred solution of the diol (9·8 g.) in pyridine (80 c.c.) at 0°. After a further 40 minutes at 0° the solution was poured into 5*N*-sulphuric acid (300 c.c.) containing some crushed ice. The precipitated oil was taken up in chloroform and washed with water, and the extract was then dried (Na_2SO_4) and evaporated under reduced pressure to constant weight (14·1 g., 66%). The *ω-toluene-p-sulphonate* was an almost colourless viscous oil (Found: S, 10·8. $C_{14}H_{20}O_4S$ requires S, 11·3%). A yield of only 43% was obtained when the reaction was carried out at room temperature.

The derivative was also prepared by the gradual addition of powdered potassium hydroxide (3·7 g.) to a stirred solution of the diol (2·95 g.) and toluene-*p*-sulphonyl chloride (4·3 g.) in pure chloroform

(30 c.c.) at 0°. After 24 hours, the chloroform solution was decanted, washed with ice-water, dried (Na_2SO_4), and evaporated. The ω-toluene-*p*-sulphonate (4·0 g., 62%) contained an odoriferous by-product, later recognised to be an oxide.

ω-Methanesulphonate. Methanesulphonyl chloride (1·77 g.) in carbon tetrachloride (100 c.c.) was slowly added to a stirred solution of the diol (2·0 g.) in pyridine (20 c.c.) at 0°. The solution was set aside at 0° overnight, filtered from pyridine hydrochloride, and evaporated under reduced pressure to remove pyridine and carbon tetrachloride. Chloroform (60 c.c.) was then added, and the solution was stirred with solid sodium hydrogen carbonate and a few drops of water to decompose a little residual pyridine hydrochloride. The solution was filtered and evaporated, to give a pyridine-free oil (1·45 g.). Some dimethanesulphonate (0·38 g.) was removed by crystallisation from methanol; evaporation of the solution then gave a water-soluble oil which, although containing combined sulphur, was contaminated with some unchanged diol, since it gave a small yield of the *cis*-di-*p*-nitrobenzoate, m. p. 140°, on treatment with *p*-nitrobenzoyl chloride in pyridine.

Regeneration of 3-Hydroxymethylcyclohexanol from its Derivatives.—(i) The bisphenylurethane of m. p. 162° (1·7 g.) was mixed with powdered sodium hydroxide (0·52 g.) in a 25-c.c. distilling flask and heated at ordinary pressure to a bath-temperature of 200°, water and aniline being collected; a further quantity of the latter was removed at 100°/30 mm. The *cis*-diol (0·27 g., 62%) was then collected at 200° (bath)/0·3 mm. Small portions were converted into the bis-3:5-dinitrobenzoate, m. p. 181°, dimethanesulphonate, m. p. 103·5°, and ditoluene-*p*-sulphonate, m. p. 95°, all of which were identical with the *cis*-forms previously described.

(ii) The di-*p*-nitrobenzoate of m. p. 141° (5·6 g.) was heated under reflux with 0·5*N*-methanolic potassium hydroxide (100 c.c.) for 4 hours. Water (10 c.c.) was added, and the solution was neutralised with hydrochloric acid and evaporated to dryness under reduced pressure. Extraction with chloroform then gave 1·77 g. of *cis*-diol, b. p. 115—117°/0·2 mm., n_D^{20} 1·4902. A small portion was converted into the dimethanesulphonate, m. p. 103·5°, identical with the *cis*-derivative already described. Another portion gave the *cis-bis-α-naphthylurethane*, which crystallised from benzene–light petroleum (b. p. 60—80°) in needles, m. p. 166·5° (Found: C, 74·3; H, 6·3. $C_{36}H_{34}O_4N_2$ requires C, 74·3; H, 6·0%).

(iii) The di-*p*-nitrobenzoate of m. p. 161—162° (1·6 g.) was hydrolysed in the same way and gave the *trans*-diol (0·45 g.) as a viscous oil. With methanesulphonyl chloride in pyridine, a portion gave the *trans*-dimethanesulphonate, m. p. 103°, identical with the *trans*-derivative previously described.

3-Benzoyloxymethylcyclohexanone.—A solution of chromic anhydride (0·45 g.) in acetic acid (30 c.c.), containing a few drops of water, was slowly added to a stirred solution of the ω-benzoate (1·35 g.) in acetic acid (20 c.c.), and the whole set aside overnight. Ether (300 c.c.) was then added, and the acid was washed out with water and finally with aqueous sodium hydrogen carbonate. The ethereal solution was dried (Na_2SO_4) and evaporated to give *3-benzoyloxymethylcyclohexanone* (1·3 g., 97%), b. p. 95° (bath)/0·0001 mm., n_D^{20} 1·5287 (Found: C, 72·3; H, 7·3. $C_{14}H_{16}O_3$ requires C, 72·4; H, 6·9%). The *semicarbazone* formed needles, m. p. 145°, from aqueous methanol (Found: C, 61·7; H, 6·5. $C_{15}H_{19}O_3N_3$ requires C, 62·3; H, 6·6%). The *2:4-dinitrophenylhydrazone* crystallised from ethyl acetate in yellow needles, m. p. 201° (Found: C, 55·2; H, 4·8. $C_{20}H_{20}O_6N_4$ requires C, 55·3; H, 4·9%).

Reaction of the Dimethanesulphonate with Alkali.—(i) The *cis*-dimethanesulphonate (10 g.) was heated under reflux with 4% ethanolic potassium hydroxide (200 c.c.) for 2 hours. The precipitated potassium methanesulphonate was removed, and the ethanol was distilled off through a Vigreux column (the distillate was unsaturated). The semi-solid residue was extracted with ether, to give *ethoxymethylcyclohexene* (2·6 g., 51%), b. p. 103°/102 mm., n_D^{20} 1·4500 (Found: C, 76·5; H, 11·6. $C_9H_{16}O$ requires C, 77·1; H, 11·5%).

(ii) The *cis*-dimethanesulphonate (3·8 g.) was stirred for 2½ hours at 90° with 5% aqueous sodium hydroxide (42 c.c.). The resulting clear solution was extracted once with ether, this extract being rejected, and then continuously extracted with ether for 18 hours. Evaporation of the ethereal extract gave an oil (0·43 g.), which on treatment with *p*-nitrobenzoyl chloride in pyridine furnished the di-*p*-nitrobenzoate, m. p. and mixed m. p. 161°, of the *trans*-diol.

Reaction of the Ditoluene-p-sulphonate with Alkali.—The (*cis* + *trans*)-ditoluene-*p*-sulphonate (11·6 g.) was stirred for 6 hours at 90° with 5% aqueous potassium hydroxide (120 c.c.). From the resulting emulsion, unchanged starting material (6·85 g.) was recovered; this was boiled under reflux for 16 hours with 10% aqueous potassium hydroxide (70 c.c.). Continuous ether-extraction of the combined alkaline solutions then gave 3-hydroxymethylcyclohexanol (0·75 g.), b. p. 114—117°/1 mm., and an undistillable residue (2 g.) of unattacked ditoluene-*p*-sulphonate. The glycol was characterised as the di-*p*-nitrobenzoate, m. p. 161°, identical with the *trans*-derivative previously described.

Reaction of the Dimethanesulphonates with Potassium Acetate.—(i) The *cis*-derivative (2·5 g.) was heated under reflux with anhydrous potassium acetate (4·3 g.) in ethanol (80 c.c.) for 24 hours. Water (30 c.c.) was then added to dissolve the precipitated sodium methanesulphonate, and the solution was neutralised to phenolphthalein by titration with 0·216*N*-sodium hydroxide (35·7 c.c.; corresponding to 0·87 mole of acetic acid). It was then distilled to remove ethanol, the residual aqueous solution (*A*) being reserved. The distillate, which was unsaturated and had the characteristic odour of ethoxymethylcyclohexene, was diluted with water and continuously extracted with ether for several hours. Solvent was removed from the extract through a Vigreux column, and the residue on distillation gave ethoxymethylcyclohexene (0·62 g., 51%), b. p. 105—110°/105 mm., n_D^{20} 1·4515. Extraction of the aqueous solution (*A*) with ether gave mainly the diacetate of 3-hydroxymethylcyclohexanol (0·46 g., 25%), b. p. 136—138°/28 mm., n_D^{20} 1·4538, which contained traces of an unsaturated impurity. Hydrolysis by heating with 10% aqueous potassium hydroxide, followed by continuous ether-extraction, gave the diol, characterised as the *trans*-di-*p*-nitrobenzoate, m. p. and mixed m. p. 160°.

(ii) The *trans*-dimethanesulphonate (2·5 g.) on similar treatment gave 0·3 g. of ethoxymethyl*cyclo*hexene, b. p. 120° (bath)/80 mm., and 0·7 g. of diacetate, b. p. 136—139°/30 mm., n_D^{25} 1·4522. The latter was hydrolysed and characterised as the *cis*-di-*p*-nitrobenzoate, m. p. and mixed m. p. 139—140°.

Reaction of the Dimethanesulphonate with Sodium Iodide.—The *cis*-derivative (0·75 g.), sodium iodide (2 g.), and acetone (15 c.c.) were heated in a sealed tube at 100° for 2 hours. The precipitated sodium methanesulphonate was removed and washed with acetone. Evaporation of the filtrate and washings gave a semi-solid residue which was diluted with water and extracted with ether. The extract was washed with aqueous sodium thiosulphate to remove free iodine, dried (Na_2SO_4), and evaporated to an oil, which on distillation furnished *3-iodomethylcyclohexyl iodide* (0·5 g.) as an almost colourless liquid, b. p. 65—70° (bath)/0·0006 mm., n_D^{25} 1·6233 (Found: I, 71·6. $C_7H_{12}I_2$ requires I, 72·5%). It gradually decomposed on storage.

Reaction of the Dimethanesulphonate with Lithium Chloride.—The *cis*-derivative (1·0 g.), lithium chloride (0·75 g.), and ethanol (35 c.c.) were boiled under reflux for 40 hours. The alcohol was then distilled off (the distillate was unsaturated), and the residue was diluted with water and extracted with ether. Removal of solvent from the dried (Na_2SO_4) extract gave *chloromethylcyclohexene* (0·37 g., 81%), b. p. 215—220°, n_D^{25} 1·4840 (Found: Cl, 28·9. $C_7H_{11}Cl$ requires Cl, 27·2%).

3-Chloromethylcyclohexanol.—(i) 3-Hydroxymethyl*cyclo*hexanol (14·5 g.; mixture of stereoisomers) was heated with fuming hydrochloric acid (30 c.c.; *d* 1·19) at 110° for 14 hours in a sealed tube. The oil was separated from the aqueous portion, and the latter was extracted with chloroform, which was then added to the oil and washed with sodium hydrogen carbonate solution, dried (Na_2SO_4), and evaporated to a liquid, distillation of which gave *3-chloromethylcyclohexanol* (13·8 g., 83%), b. p. 73°/0·5 mm., 127—130°/36 mm., n_D^{25} 1·4910 (Found: C, 56·3; H, 8·9; Cl, 24·0. $C_7H_{13}OCl$ requires C, 56·6; H, 8·8; Cl, 23·9%); a higher-boiling residue (1·9 g.) consisted of unchanged diol. Treatment of a portion of the chloride with α-naphthyl isocyanate gave a solid product which on fractional crystallisation from light petroleum (b. p. 80—100°) gave the *α-naphthylurethane*, m. p. 142°, as rosettes of fine needles (Found: N, 4·5. $C_{18}H_{20}O_2NCl$ requires N, 4·4%). From the mother-liquors there was obtained some material, m. p. *ca.* 127—128° (Found: N, 4·6%), which probably contained the other stereoisomer, but the quantity was insufficient for further purification.

(ii) Similar treatment of the *cis*-diol (1·3 g.) gave *cis*-chloromethyl*cyclo*hexanol (0·7 g.), b. p. 119—123°/30 mm., n_D^{25} 1·4858. It gave an α-naphthylurethane, m. p. 142°, identical with that described above.

(iii) The ω-toluene-*p*-sulphonate (3·0 g.; mixture of stereoisomers) and lithium chloride (1·35 g.) in ethanol (20 c.c.) were boiled under reflux for 6 hours. The solvent was then distilled off through a Vigreux column, the residue was treated with water and chloroform, and the chloroform extract was dried (Na_2SO_4) and evaporated. The chloromethyl*cyclo*hexanol (1·4 g., 90%) had b. p. 76—80°/0·5 mm., n_D^{25} 1·4913, and gave an α-naphthylurethane which was mainly the *cis*-form, m. p. 142°.

1 : 3-endo*Methyleneoxy*cyclo*hexane.*—3-Chloromethyl*cyclo*hexanol (6·7 g.; mixture of stereoisomers) was mixed to a paste with finely powdered sodium hydroxide (11 g.) and heated at 60—70°/35 mm. in a sublimation apparatus, the condensing surface being cooled with water at 0°. After 45 minutes, the hard transparent solid sublimate was collected, and on resublimation gave 1 : 3-endo*methyleneoxycyclohexane* (2·2 g., 44%), m. p. 96—97° (Found: C, 74·7; H, 10·9. $C_7H_{12}O$ requires C, 74·9; H, 10·8%). Further sublimation from the original reaction mixture gave an additional small quantity of the oxide, but prolonged heating merely resulted in contamination of the product with water. The alkaline residue, which had a very strong odour of the oxide, was dissolved in water, neutralised with hydrochloric acid, and extracted with ether. Removal of ether from the dried extracts gave an oil (2·1 g.), which was unsaturated and contained chlorine; it was not possible to obtain any pure oxide from this.

Similar treatment of the 3-chloromethyl*cyclo*hexanol (0·58 g.), from the *cis*-diol, with powdered sodium hydroxide, gave 0·21 g. of oxide.

1 : 3-*endo*Methyleneoxy*cyclo*hexane was very readily soluble in all common solvents, including cold water and cold light petroleum, and could only be satisfactorily purified by sublimation. It had a strong camphoraceous odour and was quite volatile even at ordinary temperatures, small quantities soon disappearing when exposed to the air. It was unaffected by treatment for 8 hours with methanesulphonic acid or toluene-*p*-sulphonic acid, in ether at 20° or in boiling benzene. It did not react with water in the presence of catalytic amounts of perchloric acid at 20° or 100°, but when heated with water in a sealed tube at 195° for 16 hours it gave an unsaturated oil which decomposed on attempted distillation at 100°/0·0002 mm.

Reactions of 1 : 3-endo*Methyleneoxycyclohexane with Hydrochloric Acid.*—(i) The oxide (1·05 g.) and fuming hydrochloric acid (0·8 c.c.; *d* 1·19) were heated in a sealed tube at 115° for 21 hours. The oil was separated from the aqueous portion by extraction with chloroform (3 × 7 c.c.), and the extracts were washed with sodium hydrogen carbonate solution, dried (Na_2SO_4), and evaporated. Distillation of the residue then gave *3-chloromethylcyclohexyl chloride* (1·5 g., 96%), b. p. 102—104°/23 mm., n_D^{25} 1·4940 (Found: C, 50·8; H, 7·1; Cl, 42·3. $C_7H_{12}Cl_2$ requires C, 50·3; H, 7·2; Cl, 42·4%).

(ii) The oxide (1·0 g.) was heated with fuming hydrochloric acid (2·3 c.c.) in a sealed tube for 14 hours at 112° and then worked up as in the previous experiment, to yield 3-chloromethyl*cyclo*hexanol (1·1 g., 83%), b. p. 120°/23 mm., n_D^{25} 1·4910. It gave the α-naphthylurethane, m. p. 142°, identical with that previously described.

Reactions of the ω-Toluene-p-sulphonate with Alkali.—(i) The monotoluene-*p*-sulphonate (0·64 g.) was mixed with powdered sodium hydroxide (0·6 g.) and heated at 60°/32 mm. in the sublimation apparatus used for the preparation of 1 : 3-*endo*methyleneoxy*cyclo*hexane from the chloride (see above). The yield of oxide was 0·06 g. (24%); a further amount present in the residue could not be isolated.

(ii) The monotoluene-*p*-sulphonate (7·4 g.) was stirred at 70° for 2 hours with 30% aqueous sodium hydroxide (14 c.c.). The resulting emulsion was extracted with ether, and the extract was dried (Na_2SO_4) and evaporated to an oil, from which a small amount of oxide (0·15 g.) was obtained by sublimation; the ether distillates had a strong odour of oxide, and much of the latter had probably been lost owing to its high volatility. The non-volatile residue (2·3 g.) appeared to consist of unchanged toluene-*p*-sulphonate and was recovered almost quantitatively after further treatment for 4 hours at 70° with 30% aqueous sodium hydroxide; it reacted with benzoyl chloride in pyridine, but no solid derivative could be obtained.

(iii) The monotoluene-*p*-sulphonate (3·9 g.) was heated with 0·5*N*-methanolic sodium methoxide (72 c.c.) at 60° for 8 hours; much sodium toluene-*p*-sulphonate was precipitated. Water (0·5 c.c.) was added, and the solution was neutralised with carbon dioxide and filtered. Methanol was removed by distillation through a Vigreux column (the distillate had a strong odour of the oxide), and the residue was taken up in ether, which was then dried (Na_2SO_4) and evaporated to an oil. On distillation there was obtained *3-methoxymethylcyclohexanol* (2·04 g., 67%), b. p. 78—79°/0·1 mm., n_D^{25} 1·4700 (Found: C, 66·6; H, 11·2. $C_8H_{16}O_2$ requires C, 66·6; H, 11·2%). There was an undistilled residue of unchanged monotoluene-*p*-sulphonate (0·6 g.), and some 1 : 3-*endo*methyleneoxycyclohexane (0·1 g.) was recovered from the liquid-air trap in the vacuum system.

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435. *The Fluorides of Niobium, Tantalum, Tungsten, and Rhenium.*

By H. J. Emeléus and V. Gutmann.

Tantalum trifluoride was prepared by the action of hydrogen fluoride on tantalum powder or "tantalum hydride" at 250—300°. Tantalum pentafluoride was formed simultaneously. Niobium, its "hydride," or the impure trichloride ($NbCl_{3-5}$) under similar conditions gave only the pentafluoride. The preparation of pure tungsten dibromide is described. It reacted with hydrogen fluoride at 600° forming tungsten and its hexafluoride. Rhenium trichloride reacted with hydrogen fluoride forming the metal and only traces of the volatile hexafluoride. Tungsten and rhenium metals were unattacked by hydrogen fluoride.

The fluorides of many transition elements in their lower valency states are at present very incompletely known, though often other halides of the elements in these states have been characterised. It is difficult to decide from the literature if the missing compounds are inherently unstable or if a suitable preparative method has not yet been found. Klemm (F.I.A.T. Review of German Science, 1939–46, Inorg. Chem., Vol. II, p. 15) mentioned that Ehrlich tried unsuccessfully to prepare titanium difluoride, TiF_2. The instability of vanadium and molybdenum difluorides and the preparation of molybdenum trifluoride were described recently (Emeléus and Gutmann, *J.*, 1949, 2979), but information on the lower fluorides of other transition elements was still lacking. The experiments described below were designed to throw light on the matter. They represent a study of the reaction of hydrogen fluoride with niobium, tantalum, tungsten, and rhenium, or with lower chlorides and bromides of these elements under conditions such that formation of a lower fluoride would be expected.

In the cases of niobium and tantalum only the pentafluorides are known with certainty, though Ruff and Schiller (*Z. anorg. Chem.*, 1911, **72**, 329) observed the formation of a blue "lower fluoride" on heating niobium pentafluoride in hydrogen at its boiling point. On the other hand, tantalum trichloride and tribromide and a lower niobium chloride, said to be the trichloride (Sūe, *Bull. Soc. chim.*, 1939, **6**, 830), have been prepared. Lower iodides, the composition of which has not been confirmed, have been described for both niobium and tantalum (Koeroesy, *J. Amer. Chem. Soc.*, 1939, **61**, 838). Sūe gave no analysis of the trichloride, and a number of preparations based on his method of reducing the pentachloride by hydrogen gave compounds varying in composition between $NbCl_3$ and $NbCl_4$. This niobium chloride was found to be unattacked by liquid hydrogen fluoride. With gaseous hydrogen fluoride there was no reaction below 400° and little between 400° and 500°, whereas above 500° oxidation to the pentafluoride occurred without formation of trifluoride. Niobium powder also reacted with anhydrous hydrogen fluoride at 250° and 300°, but the only product identified was the pentafluoride. This is in fact a convenient method for the preparation of the pentafluoride, which hitherto has been made by the reaction of the hygroscopic pentachloride with liquid hydrogen fluoride, or by fluorination of the metal with fluorine (Ruff and Schiller, *loc. cit.*). When niobium,

previously heated in hydrogen at 250°, was heated at the same temperature in a mixture of hydrogen and hydrogen fluoride the pentafluoride was again formed, but a very thin blue layer was observed on the residual metal; this layer could not be separated and was possibly identical with the blue substances observed by Ruff and Schiller (*loc. cit.*).

Tantalum powder reacted similarly with hydrogen fluoride. At 300° a 90% yield of the pentafluoride was obtained, but a greyish-white non-volatile and non-hygroscopic residue remained which was found to be tantalum trifluoride. The yield of trifluoride was increased somewhat when the metal was preheated in hydrogen at 250° and the product was then heated in a hydrogen–hydrogen fluoride mixture at 300°, but contamination by unchanged metal became appreciable in this case and the reaction proceeded at a much lower rate. The trifluoride neither melted nor sublimed in nitrogen or hydrogen fluoride at 650°. It was converted into the pentoxide when ignited in air and was insoluble in water and acids, except aqueous hydrofluoric acid. It was decomposed by aqua regia or hot nitric acid and also dissolved in a boiling mixture of sodium hydroxide and hydrogen peroxide. The compound has the cubic rhenium trioxide structure (Gutmann and Jack, unpublished observations) and thus resembles molybdenum trifluoride. Tantalum trifluoride could probably also be prepared from tantalum trichloride or tribromide by a method similar to that used for molybdenum trifluoride (Emeléus and Gutmann, *loc. cit.*).

Tungsten hexafluoride has been known for some time (Ruff and Eisner, *Z. anorg. Chem.*, 1907, **52**, 256; Ruff and Ascher, *ibid.*, 1931, **196**, 416) and the tetrafluoride has been described recently (Priest and Schumb, *J. Amer. Chem. Soc.*, 1948, **70**, 3378). No lower fluorides are, however, known, although the dichloride, dibromide, and di-iodide have all been recorded. Tungsten powder differed from tantalum in that it was unattacked by hydrogen fluoride up to 700°, and an attempt was therefore made to prepare lower fluorides from the other dihalides. Tungsten dichloride could not be prepared in a pure state by reduction of the hexachloride (Biltz and Fendius, *Z. anorg. Chem.*, 1928, **172**, 385) and attempts were made to obtain tungsten dibromide. The product obtained by Roscoe's method (*Annalen*, 1872, **162**, 349) was found to contain unattacked metal and higher bromides. A pure product was, however, obtained by reducing the pentabromide in hydrogen at 400—450° and heating the product in a stream of dry nitrogen at 550°. The dibromide was a greenish-yellow powder, insoluble in water and unattacked by acids except hot nitric acid, which reacted with precipitation of yellow tungsten trioxide. It resembled molybdenum dibromide in its chemical inertness. It sublimed unchanged in nitrogen above 600°, but was converted into the trioxide when ignited in air. No reaction occurred with hydrogen fluoride up to 500°, but at 550° there was a slow reaction and, at intermediate stages of the reaction, the product contained fluorine. Probably the difluoride is formed but, since it is probably non-volatile, attack on the dibromide is incomplete. At 600°, however, the reaction went to completion and hexafluoride distilled off, though it could not be separated from hydrogen fluoride by distillation (b. p. 19°). The residue in the boat was metallic tungsten and not the difluoride. The weight of metal was less than would be expected for disproportionation according to the equations:

$$3WBr_4 + 6HF \rightleftharpoons 3WF_4 + 6HBr$$

$$3WF_4 \xrightarrow{600°} 2W + WF_6$$

but this could be accounted for by sublimation of unchanged dibromide at 600°. This behaviour parallels that of the corresponding molybdenum compound (Emeléus and Gutmann, *loc. cit.*). No anhydrous trihalides of tungsten (*e.g.*, WCl_3) are known and many experiments designed to prepare them were unsuccessful.

Two simple fluorides of rhenium are known: the hexafluoride (Ruff and Kwasnik, *Z. anorg. Chem.*, 1932, **209**, 113) and the tetrafluoride (*idem*, *ibid.*, 1934, **219**, 65). Rhenium powder was unattacked by anhydrous hydrogen fluoride at 500°, and an attempt was made to prepare a lower fluoride from the trichloride. This was insoluble in liquid hydrogen fluoride. With gaseous hydrogen fluoride no reaction occurred at 100°. At 240° an intermediate product was obtained, consisting mainly of unchanged trichloride and probably some metal. At 350° reaction was complete but the product in the boat was metallic rhenium. In this case very little hexafluoride was formed and the rhenium in the residue accounted for almost all of that in the trichloride taken. The probable course of the reaction is shown by the equations:

$$ReCl_3 + 3HF \rightleftharpoons ReF_3 + 3HCl$$

$$ReF_3 \longrightarrow Re + \tfrac{3}{2}F_2$$

In this case, as in that of tungsten difluoride, there is evidence that the lower fluoride is formed under conditions when it is decomposed. The experiments thus throw some light on the stability of these compounds, though clearly some other preparative methods operating at lower temperatures will be needed to produce the lower fluorides in states of purity.

Experimental.

Reactions with Gaseous Hydrogen Fluoride.—These reactions were carried out in a platinum-lined Monel tube, the exit of which had a constriction and was water-cooled to trap any sublimate. The tube was connected to a cylinder of hydrogen fluoride by a copper T-piece, through which either nitrogen or hydrogen could be admitted to the stream of hydrogen fluoride. The tube was heated in an electric furnace, and samples for treatment were contained in a platinum boat.

Preparation and Fluorination of "Niobium Trichloride."—The pentachloride was prepared by the action of chlorine on heated niobium powder in a Pyrex tube, and the product was reduced by repeated sublimations in hydrogen through a zone of the tube heated to *ca.* 500°, as in the reduction of tungsten hexachloride to dichloride (Biltz and Fendius, *Z. anorg. Chem.*, 1928, **172**, 385). This yielded a greyish-green solid which was non-hygroscopic and non-volatile at 550°. It was analyzed for chlorine by precipitation as silver chloride after precipitation of niobium with aqueous ammonia. The niobium precipitate was ignited to pentoxide and weighed. The results for several preparations showed the product to be intermediate in compositions between $NbCl_2$ and $NbCl_3$ (Found: Nb, 53·2, 53·6, 52·0, 53·2; Cl, 47·2, 46·5, 48·1, 46·0. Calc. for $NbCl_2$: Nb, 46·7; Cl, 53·3. Calc. for $NbCl_3$: Nb, 56·7; Cl, 43·3%). When treated with anhydrous hydrogen fluoride at 500°, the chloride was converted almost completely into the volatile niobium pentafluoride, which collected near the constriction of the cooled part of the reaction tube. It was analyzed for fluorine by the Willard–Winter method (*Ind. Eng. Chem. Anal.*, 1933, **5**, 7), 50% sulphuric acid being used for decomposition, and the distilled fluoromilicic acid titrated by 0·05*N*-thorium nitrate (Found: Nb, 49·2; F, 50·5. Calc. for NbF_5: Nb, 49·5; F, 50·5%). The very small residue remaining in the platinum boat at 500° was green and contained chlorine. At 600° conversion into the pentafluoride was complete.

Fluorination of Niobium with Hydrogen Fluoride.—Niobium powder reacted with hydrogen fluoride at 250°, the volatile product being the pentafluoride and the residue unattacked metal. At 300° 3 g. of the metal were converted quantitatively into pentafluoride in 6 hours (Found: Nb, 49·6, 49·1; F, 50·2, 50·6%). This method is a useful alternative to the reaction of fluorine with niobium or of liquid hydrogen fluoride with the hygroscopic pentachloride. When the niobium was first heated at 250° in hydrogen and then at the same temperature in hydrogen–hydrogen fluoride, the pentafluoride was again formed, though in lower yield. The surface of the residual metal was coated with a thin blue layer which could not be separated. An *X*-ray powder photograph of the residue showed only lines due to the metal and no evidence could be obtained for the formation of trifluoride.

Preparation of Tantalum Trifluoride.—Tantalum powder reacted with anhydrous hydrogen fluoride below 200°, the product being a mixture of unattacked metal, tantalum pentafluoride, and probably some trifluoride. The pentafluoride could be separated by distillation in nitrogen at 250°. At 300° complete reaction of the metal occurred, about 90% yielding the volatile pentafluoride, while about 10% remained as non-volatile *tantalum trifluoride*. For analysis the trifluoride was dissolved in a mixture of sodium hydroxide and hydrogen peroxide, and tantalum determined as tantalum pentoxide. It was analyzed for fluorine by the Willard–Winter method (*loc. cit.*) (Found: Ta, 75·4, 75·8; F, 22·9, 24·1. TaF_3 requires Ta, 76·1; F, 23·9%). The volatile pentafluoride was collected near the constriction of the tube and was analyzed similarly after dissolution in sodium hydroxide (Found: Ta, 65·4; F, 34·4. Calc. for TaF_5: Ta, 65·7; F, 34·3%). The reaction followed a similar course when the metal was preheated in hydrogen at 250° and then fluorinated with hydrogen–hydrogen fluoride, but was appreciably slower.

Preparation of Tungsten Dichloride and Dibromide.—Tungsten powder, previously heated in hydrogen to 1000° to remove any oxidic impurities, was converted into the hexachloride by heating it in chlorine in a Pyrex tube, and this salt was reduced by hydrogen under the conditions given by Biltz and Fendius (*loc. cit.*). The product was not pure, however, and appeared to contain higher chlorides. Tungsten was determined as tungsten trioxide after treatment of the chloride with nitric acid, evaporation to dryness, and ignition at 850°. For halogen determination the substance was dissolved in a mixture of sodium hydroxide and hydrogen peroxide and evaporated to dryness, and the residue digested with 20% nitric acid (Cooper and Wardlaw, *J.*, 1932, 630). Tungsten trioxide was filtered off and chloride determined as silver chloride in the filtrate after addition of phosphoric and nitric acids (Found: W, 70·1, 68·9; Cl, 30·7, 32·0. Calc. for WCl_2: W, 72·2; Cl, 27·8%).

In the preparation of tungsten dibromide, tungsten was first brominated at 600° by bromine vapour carried in a nitrogen stream. The pentabromide sublimed and was then reduced by heating it in hydrogen as described by Biltz and Fendius (*loc. cit.*) for the preparation of the dichloride. It was necessary to avoid temperatures above 500°, as otherwise metallic tungsten was formed. The reduced material was then heated to 550° in a stream of purified nitrogen to remove more volatile higher halides. A yellowish-green solid—pure tungsten dibromide—remained. It was analyzed as described for the dichloride (Found: W, 53·2; Br, 46·9. Calc. for WBr_2: W, 53·5; Br, 46·5%).

Reaction of Tungsten Dibromide with Hydrogen Fluoride.—Reaction commenced at *ca.* 550° and was incomplete even after 30 hours' heating at 580°. At 600° the dibromide commenced to sublime. The non-volatile product of the reaction at 600° contained no fluorine and was shown analytically and by an *X*-ray powder photograph to consist of tungsten. It was assumed that tungsten hexafluoride was the other reaction product. A blue layer of tungsten oxides was observed near the outlet of the reaction

tube, which was probably produced by hydrolysis of tungsten hexafluoride. In one experiment the tungsten dibromide which sublimed unchanged was recovered and weighed. The weight of dibromide used was 2·4816 g., that of sublimed unchanged dibromide was 0·4178 g., and that of tungsten metal remaining in the boat was 0·6920 g. This corresponds to a 94% recovery of tungsten on the basis of the equation already given. It was shown that tungsten powder was unattacked by anhydrous hydrogen fluoride up to 700°.

Preparation and Fluorination of Rhenium Trichloride.—Rhenium trichloride was prepared as described by Geilmann, Wrigge, and Biltz (*Nachr. Ges. Wiss. Göttingen, Math.-Phys. Kl.*, 1932, 579). Metallic rhenium, previously heated to redness in hydrogen, was heated in a porcelain boat in a tube furnace, first in nitrogen and then in purified chlorine. The black distillate of pentachloride was distilled into the first of a series of Pyrex bulbs, in which it was carefully heated in dry nitrogen to bring about decomposition into the trichloride and chlorine. The completion of the decomposition was indicated by the absence of brown vapour when the solid was heated gently. The residual trichloride sublimed when heated more strongly, giving a green vapour, and could be purifiedi n this way. It was obtained in a yield of about 60%. It was analyzed for chlorine as silver chloride, after oxidation of the rhenium to per-rhenate as described by Geilmann and Lange (*Z. anorg. Chem.*, 1937, **234**, 289) (Found: Cl, 36·5, 36·3. Calc. for $ReCl_3$: Cl, 36·4%). Rhenium trichloride was insoluble in liquid hydrogen fluoride. No reaction occurred with gaseous hydrogen fluoride at 100°. When the trichloride was heated at 240° an intermediate product was obtained which, however, consisted mainly of unchanged trichloride. Above 350° reaction of the trichloride, which is stable at 500° in nitrogen, was complete and metallic rhenium remained in the boat. This was identified by an *X*-ray powder photograph. Traces of a fluoride appeared to be present, however, since on exposure to air in glass tubes the latter were slightly etched within a few weeks. No fluorine was found on analysis. The amount of rhenium remaining corresponded almost quantitatively to that contained in the trichloride, as is shown by the following results:

$ReCl_3$ taken (g.)	0·2244	0·4288	0·3000
Re in $ReCl_3$ taken (g.)	0·1468	0·2729	0·1910
Re from the reaction (g.)	0·1440	0·2612	0·1885

Only traces of the volatile hexafluoride were formed, probably by a secondary reaction of the fluorine set free in the thermal decomposition of rhenium trifluoride formed as an intermediate.

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436. *Peroxides of Tetrahydrocarbazole and Related Compounds. Part I. Tetrahydrocarbazolyl Hydroperoxide.*

By R. J. S. BEER, L. MCGRATH, and ALEXANDER ROBERTSON.

The preparation and properties of 1:2:3:4-tetrahydrocarbazolyl hydroperoxide are described. With aqueous sodium hydroxide this peroxide gave a compound, m. p. 340°, along with a small amount of *cyclo*pentane*spiro*-2-ϕ-indoxyl, which was also formed by treatment with ferrous ions in acid solution. With sodium hydrosulphite (dithionite) it gave a compound, m. p. 153°, identical with so-called "10-hydroxy-1:2:3:10-tetrahydrocarbazole" of Plant and Tomlinson (*J.*, 1933, 298). Reduction of the peroxide over a palladium catalyst regenerated 1:2:3:4-tetrahydrocarbazole whilst a platinum catalyst gave rise to the same hydroxy-hexahydrocarbazole as was obtained by hydrogenation of the compound, m. p. 153°. The structures of the peroxide and of the related compound, m. p. 153°, are discussed and possible mechanisms for the peroxidation process elaborated.

Catalytic hydrogenation of *cyclo*pentane*spiro*-2-ϕ-indoxyl afforded a tetrahydro-derivative which readily forms a peroxide.

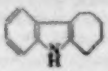
The compound, m. p. 115°, regarded by Plant and Tomlinson (*loc. cit.*) as 11-hydroxy-2:3:4:11-tetrahydrocarbazole, is shown to be 1-hydroxy-1:2:3:4-tetrahydrocarbazole.

IN the course of attempts to purify 6:7-dimethoxy-1:2:3:4-tetrahydrocarbazole by crystallisation from light petroleum–ethyl acetate it was found that the compound readily absorbed atmospheric oxygen, giving rise to a crystalline peroxide. This unexpected and surprisingly ready reaction leading to a relatively stable peroxide was subsequently found to occur also with 1:2:3:4-tetrahydrocarbazole and its 6:7-methylenedioxy-derivative (*J.*, 1949, 2061; *Nature*, 1949, **164**, 362) and the present communication deals with the results of our preliminary examination of the chemical properties of 1:2:3:4-tetrahydrocarbazole peroxide which, on account of its accessibility, was an obvious choice for initial study.

The formation of 1:2:3:4-tetrahydrocarbazole peroxide takes place in light petroleum in the absence of a catalyst and, although it appears to be accelerated by irradiation with ultraviolet light, proceeds as satisfactorily in darkness as in laboratory illumination. Although the

average yield of purified peroxide is about 40%, the yield of crude product is generally much higher. Of considerable interest is the observation that 9-methyl- and 9-acetyl-1 : 2 : 3 : 4-tetrahydrocarbazole appear to resist attack under the conditions employed in this work.

(I.)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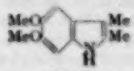
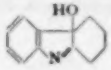

(III.)

Curiously, 2 : 3-*cyclo*penteno- (I) and 2 : 3-*cyclo*hepteno-indole (II) (Perkin and Plant, *J.*, **1923**, **123**, 3244; **1926**, 2586) have not yielded crystalline peroxides under our conditions although in experiments with added catalysts (*e.g.*, traces of a peroxide of tetrahydrocarbazole, cobalt stearate) decomposition of these indoles occurs and the amorphous products obtained have sometimes given feebly positive tests for peroxides. Similarly, 5 : 6-dimethoxy-2 : 3-dimethylindole (III) (*J.*, **1949**, 2061) has afforded a product containing traces of peroxide and it seems likely that, with the discovery of appropriate conditions, simple indoles and even pyrroles may be induced to yield isolable peroxides. In this connection it may be noted that peroxide formation by this type of compound may possibly be of considerable biological significance in the phytochemical production of complex basic substances as well as in the formation of the melanins (*J.*, **1948**, 2223).

1 : 2 : 3 : 4-Tetrahydrocarbazole peroxide, $C_{12}H_{13}O_2N$, which melts between 124° and 129° with vigorous decomposition accompanied by the emission of a vivid blue flash, liberates iodine immediately from acidified aqueous potassium iodide and differs from the parent tetrahydrocarbazole and the indoles generally in being readily soluble in dilute aqueous mineral acids. With nitrous acid the peroxide appears to behave as a secondary amine. It also shows weakly acidic properties and although it is rapidly decomposed by alkalis some peroxidic material can be recovered from an alkaline solution, indicating that the compound is, in fact, a hydroperoxide containing the group ·O·OH. From the reaction of the peroxide with aqueous sodium hydroxide two products have been isolated, the chief of which is a high-melting substance, $C_{12}H_{11}ON$, m. p. about 330°, showing both basic and acidic properties. This compound, which will be discussed in a later communication, is accompanied by small amounts of a yellow compound identical (*Nature*, *loc. cit.*) with the "11-hydroxytetrahydrocarbazolenine," m. p. 79°, (IV) or (V), of Perkin and Plant (*J.*, **1923**, **123**, 689) which has recently been formulated as the *cyclo*pentane*spiro*-2-3-indoxyl (VI) by Plant and Robinson (*Nature*, **1950**, **165**, 36) and by Witkop (*J. Amer. Chem. Soc.*, **1950**, **72**, 614). The same compound, m. p. 79°, was obtained in low yield by the action of acetic acid and iron powder on the peroxide but in this case it was accompanied by the colourless "2 : 3-dihydrocarbazole," m. p. 293—295°, formulated as (VII) by Plant and Tomlinson (*J.*, **1931**, 3324; **1933**, 298) together with a second, yellow substance, m. p. 245°, which appears to have the empirical formula $C_{24}H_{24}ON_2$ or $C_{24}H_{22}ON_2$.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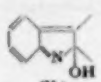
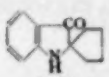
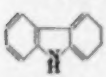
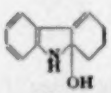
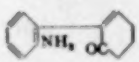

(V.)


(VI.)


(VII.)


(VIII.)


(IX.)

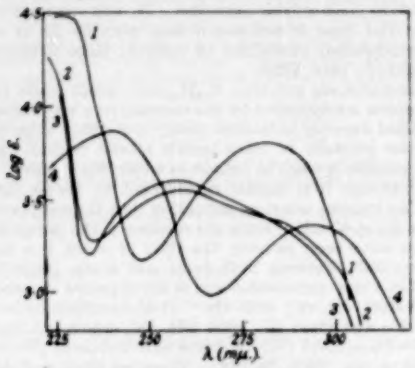
With alkaline aqueous sodium hydrosulphite (dithionite), tetrahydrocarbazolyl hydroperoxide gave rise to a compound, m. p. 153°, which was identical with the so-called 10-hydroxy-1 : 2 : 3 : 10-tetrahydrocarbazole (VIII) of Plant and Tomlinson (*loc. cit.*). Like the parent peroxide this compound is also basic and decomposes in dilute sulphuric acid to mixed products from which the "2 : 3-dihydrocarbazole," m. p. 293—295°, can be isolated in small yield. In addition, the acidic decomposition of the peroxide has afforded a small amount of a non-basic substance, m. p. about 150°, which has not yet been obtained pure.

Reduction of tetrahydrocarbazolyl hydroperoxide with hydrogen and a palladium–charcoal catalyst regenerated 1 : 2 : 3 : 4-tetrahydrocarbazole but with a platinum oxide catalyst a compound $C_{12}H_{11}ON$ was obtained, identical with the hydrogenation product of the compound,

m. p. 153°. This product is clearly a hydroxyhexahydrocarbazole since on treatment with mineral acids it readily lost water giving rise to 1 : 2 : 3 : 4-tetrahydrocarbazole.

From the foregoing results it is apparent that 1 : 2 : 3 : 4-tetrahydrocarbazolyl hydroperoxide and the compound, m. p. 153°, are structurally very closely related, a view supported by the close similarity of their ultra-violet absorption curves (see Fig. 1) which differ markedly from that of 1 : 2 : 3 : 4-tetrahydrocarbazole. Further, it is clear that in the formation of the peroxide some modification of the conjugated system present in the parent tetrahydrocarbazole takes place, in keeping with the appearance of basic properties in the peroxide. The formula (VIII) was assigned to the compound, m. p. 153°, by Plant and Tomlinson (*loc. cit.*) to account for its behaviour as an aromatic primary amine which could be diazotised, *i.e.*, the compound behaved as the isomeride (IX) in mineral acid solution and on this basis 1 : 2 : 3 : 4-tetrahydrocarbazolyl hydroperoxide and its hydrogenation product, which is also obtained from the compound, m. p. 153°, would be represented respectively by formulæ (X) and (XI). The

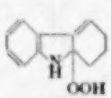
FIG. 1.



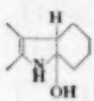
1, 1 : 2 : 3 : 4-*Tetrahydrocarbazole*. 2, 1 : 2 : 3 : 4-*Tetrahydrocarbazole peroxide*. 3, *Compound, m. p.* 153° (11-*hydroxytetrahydrocarbazolenine or* 10-*hydroxy*-1 : 2 : 3 : 10-*tetrahydrocarbazole*). 4, *Dihydro-derivative of* 3.

(*All spectroscopic measurements were made in alcoholic solution.*)

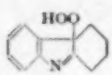
formulæ (VIII), (X), and (XI) for these compounds are in agreement with their instability in mineral acid solution.



(X.)



(XI.)



(XII.)

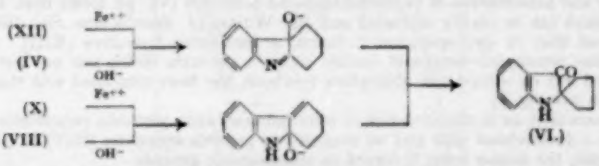
In a recent communication Patrick and Witkop (*J. Amer. Chem. Soc.*, 1950, **72**, 633) have briefly described the preparation of a compound, m. p. 159°, by catalytic oxidation of tetrahydrocarbazole followed by mild hydrogenation. From the data for its ultra-violet absorption spectrum this compound, which the foregoing authors regard as being identical with the so-called 10-hydroxy-1 : 2 : 3 : 10-tetrahydrocarbazole, would appear to be identical with the product of m. p. 153° obtained by us. In this connection it is of interest that, prepared by the method of Plant and Tomlinson (*loc. cit.*), this compound was found to have m. p. 153° except on one occasion when a sample was obtained with m. p. 158·5°. On being kept overnight, however, this material reverted to the lower-melting form, but it is not yet clear whether the compound is dimorphic since the melting point seems to vary somewhat with the rate of heating. On the basis of its infra-red absorption spectrum Patrick and Witkop (*loc. cit.*) regard this compound as being authentic 11-hydroxytetrahydrocarbazolenine (IV) and it is clear that if

this view proves to be correct then 1 : 2 : 3 : 4-tetrahydrocarbazole peroxide must have the corresponding structure (XII). Without giving experimental details Patrick and Witkop (*loc. cit.*) state that on decomposition with acid, heat, or acetic anhydride, their compound, m. p. 159°, affords an 85% yield of *cyclo*pentane*spiro*-2-ϕ-indoxyl (VI) together with a substance, m. p. 255° (and after resolidification m. p. 313°), which they regard as being identical with " 2 : 3-dihydrocarbazole," m. p. 293—295° (Plant and Tomlinson, *loc. cit.*), and to which they assign the empirical formula $C_{24}H_{18}N_2$ despite the fact that their analytical results * are in better agreement with $C_{24}H_{20}N_2$. In our experiments we have invariably failed to isolate *cyclo*pentane*spiro*-2-ϕ-indoxyl by the action of acids under a wide variety of conditions (except in the presence of iron) either from the peroxide of 1 : 2 : 3 : 4-tetrahydrocarbazole or from the compound m. p. 153°, and on the view, which we maintain, that this compound, m. p. 153°, is identical with Patrick and Witkop's substance, m. p. 159°, we are unable at present to account for the findings of these authors. Moreover, specimens of the so-called 2 : 3-dihydrocarbazole prepared by the method of Plant and Tomlinson (*loc. cit.*) and from the peroxide have had the m. p. 293—295° reported by the original authors.

In the decomposition of 1 : 2 : 3 : 4-tetrahydrocarbazolyl hydroperoxide with alkali, and with acetic acid and iron powder, it seemed feasible that the *cyclo*pentane*spiro*-2-ϕ-indoxyl, which in neither case is the major product, is formed by way of the compound, m. p. 153°. Whilst under alkaline conditions this mechanism may obtain since, as Plant and Tomlinson (*loc. cit.*) showed, " 10-hydroxy-1 : 2 : 3 : 4-tetrahydrocarbazole " readily yields the ϕ-indoxyl with alkalis, it seems to be highly improbable when the medium is acetic acid containing iron powder because with hot acetic acid the compound, m. p. 153°, as well as the peroxide of tetrahydrocarbazole, rapidly form the " 2 : 3-dihydrocarbazole," m. p. 293—295°, unaccompanied by detectable amounts of the ϕ-indoxyl. Since the difference in behaviour of 1 : 2 : 3 : 4-tetrahydrocarbazolyl hydroperoxide towards acetic acid in the presence or absence of iron might be due to the action of the ferrous ion which is known to catalyse the decomposition of peroxides (see Waters, *Ann. Reports*, 1945, **42**, 136) the peroxide was treated with cold dilute sulphuric acid containing ferrous sulphate. A rapid reaction ensued and the *spiro*-ϕ-indoxyl was isolated in approximately the same yield as in the experiments with iron powder and alcoholic acetic acid. On the other hand, the presence of ferrous sulphate did not materially affect the action of cold dilute sulphuric acid on the compound, m. p. 153°. By analogy with the Haber–Weiss theory of the metal-catalysed decomposition of hydrogen peroxide (see, *e.g.*, Waters, *loc. cit.*) the action of ferrous ions on the peroxide of 1 : 2 : 3 : 4-tetrahydrocarbazole may be considered to be :

$$\text{R·O·OH} + \text{Fe}^{++} \longrightarrow (\text{R·O})^{-} + {}^{\cdot}\text{OH} + \text{Fe}^{+++}$$

The subsequent rearrangement of the anion $(\text{R·O})^{-}$, which presumably is also formed by the action of alkali on the compound, m. p. 153° (the alcohol R·OH), to give *spiro*-ϕ-indoxyl (VI) is more easily understandable on the basis of formula (XII) rather than (X) for the peroxide :

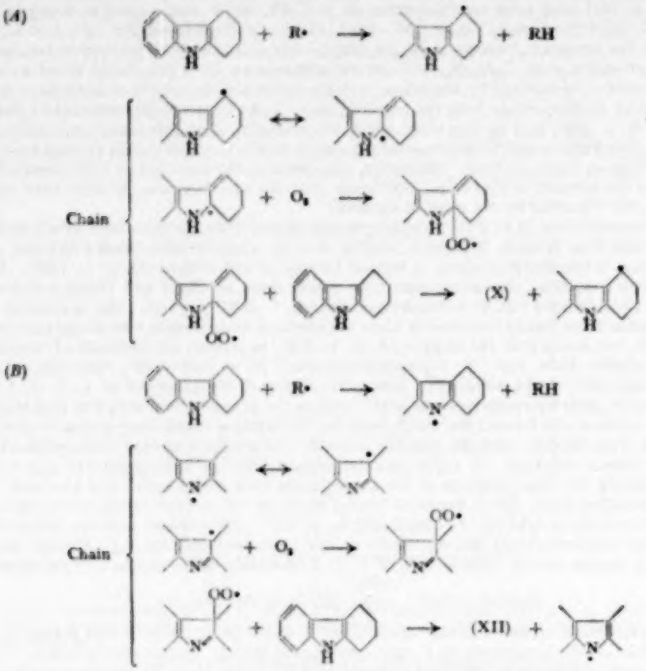


Thus the metal-catalysed decomposition of the peroxide may be considered to afford indirect support for the carbazolenine structure (XII) for this compound. Additional indirect support for this structure can be adduced from a consideration of the mechanism of peroxidation which, in common with other autoxidation processes, may be assumed to be a radical chain reaction. For this, two mechanisms are envisaged of which one (*A*) leads to structure (X) for the peroxide and the other (*B*) to (XII).

The mechanism (*B*) provides a feasible explanation of the observation that peroxidation of *N*-substituted 1 : 2 : 3 : 4-tetrahydrocarbazoles, *e.g.*, 9-methyl and 9-acetyl derivatives, does not occur. Nevertheless, on the basis of structure (XII) for the peroxide two difficulties arise. In the first place the peroxide appears to behave as a secondary amine towards nitrous

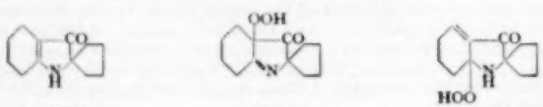
* Patrick and Witkop state that calculated values for $C_{24}H_{18}N_2$ are C, 85·25; H, 6·51; N, 8·3%, whereas these should be C, 86·23; H, 5·39; N, 8·4%.

acid and, in the second, the corresponding alcohol, m. p. 153°, behaves as a primary amine towards the same reagent. Further experiments designed to resolve these difficulties and to lead to a final decision between the two structures (X) and (XII) for the peroxide are in progress.



During our examination of *cyclo*pentane*spiro*-2-*ψ*-indoxyl (VI) we found that, as expected, the compound can be readily oximated and, like Witkop (*J. Amer. Chem. Soc.*, 1950, **72**, 614), we observed that on hydrogenation it formed a tetrahydro-derivative (XIII). In benzene solution this tetrahydro-compound readily forms a peroxide which has not yet been fully investigated but its ultra-violet absorption spectrum has been compared with that of related compounds (see Fig. 2).

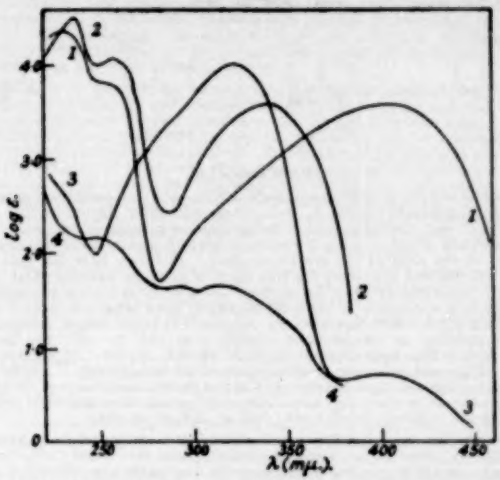
It appears that, as in the formation of tetrahydrocarbazole peroxide, peroxidation is accompanied by a double-bond shift and we suggest two possible structures (XIV) or (XV) for this new peroxide, the former being favoured on spectroscopic grounds.



(XIII.) (XIV.) (XV.)

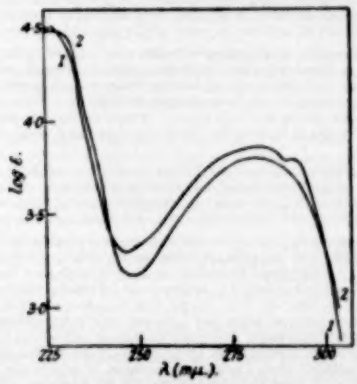
For comparison with the compound, m. p. 153°, (VIII) or (IV), we prepared the isomeric compound, m. p. 115°, from 9-benzoyl-1 : 2 : 3 : 4-tetrahydrocarbazole by the method of Plant and Tomlinson (*loc. cit.*) who ascribed to it formula (XVI). The ultra-violet absorption spectrum of this compound, however, closely resembled that of 1 : 2 : 3 : 4-tetrahydrocarbazole (see Fig. 3) and hence it seemed that in all probability the compound was (XVII) or (XVIII)

FIG. 2.



1, cyclo*Pentane*spiro-2-ψ-*indoxyl*. 2, N-*Acetyl*cyclo*pentane*spiro-2-ψ-*indoxyl*. 3, *Tetrahydro*cyclo*pentane*spiro-2-ψ-*indoxyl*. 4, *Peroxide of* 3.

FIG. 3.

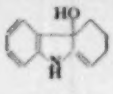


1, " 11-*Hydroxy*-2 : 3 : 4 : 11-*tetrahydrocarbazole*," m. p. 115° (1-*hydroxy*-1 : 2 : 3 : 4-*tetrahydrocarbazole*). 2, 1 : 2 : 3 : 4-*Tetrahydrocarbazole*.

rather than (XVI). That it is 1-hydroxy-1 : 2 : 3 : 4-tetrahydrocarbazole (XVII) is shown by the fact that it is formed by reduction with lithium aluminium hydride of 1-keto-1 : 2 : 3 : 4-tetrahydrocarbazole (XIX), which was prepared by the unambiguous method of Coffey (*Rec. Trav. chim.*, 1923, **42**, 528) as modified by Kent (*J.*, 1935, 976).

The conversion of 9-benzoyl-1 : 2 : 3 : 4-tetrahydrocarbazole into 1-hydroxy-1 : 2 : 3 : 4-tetrahydrocarbazole, by treatment with bromine and then aqueous ammonia followed by debenzoylation, finds a close analogy in the production of 3-methyl-2-hydroxymethylindole

from 9-acetyl-2 : 3-dimethylindole by a similar series of reactions (Plant and Tomlinson, *J.*, 1933, 955; cf. Taylor, *Helv. Chim. Acta*, 1950, **33**, 168).



(XVI.)

(XVII.)

(XVIII.)

(XIX.)

Experimental.

1 : 2 : 3 : 4-*Tetrahydrocarbazolyl Hydroperoxide* (X or XII).—(*a*) A warm filtered solution of 1 : 2 : 3 : 4-tetrahydrocarbazole (Rogers and Corson, *J. Amer. Chem. Soc.*, 1947, **69**, 2910) (2 g.) in light petroleum (b. p. 60—80°) (200 ml.) was allowed to cool in the presence of atmospheric oxygen. After a somewhat variable period (generally about ½ hour) the solution became opaque and then began to deposit the crystalline *peroxide* on the sides of the containing flask. 18 Hours later the solid (1·5—1·9 g.) was dislodged and isolated without disturbing the thin layer of resinous material which had formed on the bottom of the flask. Recrystallisation of the peroxide was effected as rapidly as possible by the addition of hot ethyl acetate to a suspension of the solid in boiling light petroleum until a clear solution was obtained. On cooling this solution deposited the compound in large, almost colourless shining tablets, which decomposed violently at temperatures varying from 124° to 129°, the decomposition being accompanied by a flash of blue light (Found: C, 70·7; H, 6·7; N, 7·0. $C_{12}H_{13}O_2N$ requires C, 70·9; H, 6·4; N, 6·9%). The yield of recrystallised product varied considerably. A high yield of the crude peroxide was associated with a comparatively high yield of purified material (*e.g.*, 0·95 g. of recrystallised peroxide from 1·9 g. of crude product) and, as sometimes happened, when the crude product was obtained in poor yield, this gave a relatively much lower yield of purified peroxide.

(*b*) A current of air was aspirated through a solution of 1 : 2 : 3 : 4-tetrahydrocarbazole (2 g.) in light petroleum (200 ml.) kept at just below its boiling point for 1 hour. The crystalline peroxide usually separated after about 30 minutes' aeration and in favourable cases the yield of purified product was equal to the optimum yields obtained by method (*a*). Occasionally, however, extensive decomposition of the carbazole or its peroxide took place and an amorphous tan powder was obtained which could not be crystallised and had a low and indefinite m. p. For routine preparations method (*a*) was preferred.

In these experiments commercial samples of light petroleum were employed and, although the use of other solvents has not yet been extensively investigated, it has been found that peroxidation proceeded normally in re-distilled *n*-hexane whereas in benzene only small amounts of a very crude peroxide were obtained. With ether as solvent in method (*a*) very slight peroxidation occurred.

1 : 2 : 3 : 4-Tetrahydrocarbazole hydroperoxide liberates iodine instantaneously from acidified aqueous potassium iodide and dissolves easily in dilute aqueous mineral acids, forming yellow solutions which rapidly become opaque and then deposit a brown amorphous precipitate. Addition of sodium nitrite to a solution of the peroxide in dilute hydrochloric acid at 0° causes the separation of a bright yellow viscous oil which can be extracted with ether. Although large crystals of the peroxide are only slowly attacked by aqueous sodium hydroxide the finely powdered compound readily forms a faintly yellow solution.

Decomposition of **1 : 2 : 3 : 4-*Tetrahydrocarbazolyl Hydroperoxide***.—(a) *With alkali*. Rapid dissolution of the peroxide in 2*N*-aqueous sodium hydroxide followed by immediate neutralisation with 2*N*-sulphuric acid gives a sticky precipitate which, on being thoroughly washed with water, is obtained as a tan-coloured powder giving a positive peroxide reaction with acidified aqueous potassium iodide.

When a solution of the peroxide (2·8 g.) in aqueous sodium hydroxide (100 ml.) was kept at room temperature for 14 hours and then neutralised with dilute sulphuric acid and the resulting microcrystalline precipitate (2·5 g.) crystallised from hot alcohol, a *substance* was obtained in shining light brown rectangular plates, m. p. 330° (decomp.), which retained their colour on repeated recrystallisation (Found: C, 77·8, 77·6; H, 5·9, 6·5; N, 7·4. $C_{12}H_{11}ON$ requires C, 77·8; H, 5·9; N, 7·6%). This product is soluble in both dilute mineral acids and aqueous alkalis but is very sparingly soluble in water or in aqueous sodium hydrogen carbonate. The neutral liquor left on the separation of this ampholyte showed the characteristic green fluorescence of *cyclo*pentane*spiro*-2-ϕ-indoxyl (VI) (Perkin and Plant, *loc. cit.*). This indoxyl was isolated from another experiment in which the peroxide (1 g.) was warmed with 2*N*-sodium hydroxide (25 ml.) on the steam-bath for 20 minutes. The yellow solution quickly became opaque and then deposited brown resinous material. Repeated extraction of the cooled reaction mixture with ether gave a yellow gum from which the ϕ-indoxyl was extracted by boiling light petroleum. Recrystallised from the same solvent, it formed bright yellow, compact prismatic needles (50 mg.), m. p. 78—79°, undepressed on admixture with an authentic specimen (Found: C, 77·05; H, 6·9; N, 7·5. Calc. for $C_{12}H_{13}ON$: C, 77·0; H, 6·95; N, 7·5%). On filtration and neutralisation, the alkaline liquor left after the separation of *cyclo*pentane*spiro*-2-ϕ-indoxyl deposited a microcrystalline powder (600 mg.) which, on crystallisation from hot alcohol, gave the substance, m. p. 330° (decomp.).

(b) *With alkaline sodium dithionite*. When a mixture of powdered peroxide (1 g.), ether (50 ml.), and *n*-sodium hydroxide (20 ml. containing 2 g. of sodium dithionite) was agitated, the solid dissolved in the course of 10 minutes. One hour later the ethereal layer was separated and the aqueous liquor extracted several times with fresh ether. Concentration of the combined, dried ethereal solutions gave

colourless crystals (530 mg.), m. p. 147—149°, followed by a further small amount of less pure material. Recrystallised from benzene this product gave "10-hydroxy-1 : 2 : 3 : 10-tetrahydrocarbazole" (VIII or IV) in colourless prisms, m. p. 153—154°, identical with an authentic specimen (Plant and Tomlinson, *loc. cit.*) (Found: C, 77·2; H, 7·0; N, 7·4. Calc. for $C_{12}H_{13}ON$: C, 77·0; H, 6·95; N, 7·5%). Like the authentic compound this product from the peroxide was readily soluble in dilute mineral acids, and in acid solution behaved as a primary aromatic amine.

(c) *With alcoholic acetic acid and iron.* The reaction between the peroxide (1 g.), iron powder (5 g.), and acetic acid (20 ml.) in alcohol (25 ml.) was initiated by gentle warming and then allowed to proceed spontaneously until it subsided in about 5 minutes. After having then been heated on the steam-bath for 7 minutes the reaction mixture was filtered and the residue of iron and ferrous acetate was well washed with several small portions of hot alcohol. The combined filtrates and washings were diluted with water and extracted several times with ether, and the ethereal extracts were concentrated until solid began to separate. After cooling, the yellow product (0·36 g.) was collected and crystallised from much benzene, giving a mixture (50 mg.) of colourless and yellow crystals. The colourless material was separated manually and then recrystallised from benzene, giving "2 : 3-dihydrocarbazole," m. p. 293—295°, identical with an authentic specimen (Plant and Tomlinson, *loc. cit.*) (Found: C, 85·15; H, 6·5; N, 8·1. Calc. for $C_{12}H_{13}N$ or $C_{24}H_{26}N_2$: C, 85·2; H, 6·5; N, 8·3%).

Concentration of the benzene mother-liquor left on separation of the mixed crystals gave a homogeneous yellow product (0·25 g.), m. p. 238—240°, which on recrystallisation from the same solvent furnished a *substance* in bright yellow prisms, m. p. 245° (Found: C, 79·8, 79·9; H, 6·1, 6·5; N, 8·4. *M* (Rast), 367. $C_{24}H_{24}ON_2$ requires C, 80·9; H, 6·7; N, 7·9%; *M*, 356. $C_{24}H_{24}ON_2$ requires C, 80·4; H, 7·3; N, 7·8%; *M*, 358).

Evaporation of the aqueous alcohol–acetic acid liquor left after separation of the crude mixed solid, followed by distillation of the product in a high vacuum, gave *cyclo*pentane*spiro*-2-ϕ-indoxyl as a yellow oil (0·2 g.) (bath-temp. 115—130°/0·5 mm.) which solidified and then formed yellow prisms, m. p. and mixed m. p. 79°, from light petroleum.

(d) *With dilute sulphuric acid.* On being heated on the steam-bath the pale yellow solution of the powdered peroxide (2 g.) in 2*N*-sulphuric acid (200 ml.) rapidly darkened and deposited a reddish-black resin. One hour later the solution was decanted, filtered, cooled, and extracted with ether. Evaporation of the ethereal extracts left a crystalline product which, after trituration with benzene to remove traces of resin, had m. p. 147—149° after sintering at about 130°. Recrystallisation of this substance (0·34 g.) has not as yet given a compound with a well-defined m. p.; nevertheless, it is distinguished from "10-hydroxy-1 : 2 : 3 : 4-tetrahydrocarbazole," m. p. 153°, in being non-basic.

The dark resin obtained in the foregoing experiment was washed and triturated with warm alcohol, which removed tarry impurities and gave a yellow solid from which "2 : 3-dihydrocarbazole" was isolated by repeated extraction with boiling benzene, followed by concentration of the combined extracts. The compound formed colourless prisms (140 mg.), m. p. 289—292° undepressed on admixture with the authentic compound.

When a solution of the peroxide (1 g.) in 2*N*-sulphuric acid was kept at room temperature for 24 hours, filtered from the brown amorphous resin, and extracted with ether, a colourless product (260 mg.), m. p. 125° to 140°, was obtained which, on recrystallisation from benzene, formed colourless prisms, m. p. about 148° after sintering at 130°. Detectable amounts of the *cyclo*pentane*spiro*-2-ϕ-indoxyl were not present in the reaction product.

(e) *With dilute sulphuric acid containing ferrous sulphate.* The powdered peroxide (1 g.) dissolved rapidly in an agitated solution of ferrous sulphate (1 g.) in 2*N*-sulphuric acid (50 ml.), and the resulting turbid yellow solution soon became green and deposited a solid. 15 Minutes later this product was isolated and washed with water, and the combined filtrate and washings were extracted with ether. Evaporation of the dried extracts gave *cyclo*pentane*spiro*-2-ϕ-indoxyl (160 mg.), m. p. 75—79° after purification from light petroleum.

Action of 2N-Sulphuric Acid on Compound, m. p. 153°.—On being kept at room temperature for 1 hour a solution of this compound (0·9 g.) in 2*N*-sulphuric acid (80 ml.) deposited an amorphous yellow solid (0·52 g.) which was collected and 18 hours later a further quantity (0·3 g.) separated. The acidic filtrate was then extracted with ether but evaporation of the extracts gave only a trace of gummy product.

The first crop of solid was extracted with boiling ether and the filtered extract evaporated leaving a yellow gum which was then extracted with several portions of boiling light petroleum (b. p. 60—80°). On concentration the combined light petroleum extracts gave a yellow powder, melting indistinctly from 120° to 200°, and further concentration of the mother-liquor afforded a second crop of similar appearance which softened at about 80° and melted at about 120°. Spontaneous evaporation of the residual light petroleum liquors left only a trace of a yellow gum. The second crop of yellow reaction product contained similar material, m. p. 120—150°, but the ϕ-indoxyl was not isolated in this experiment or when the compound, m. p. 153°, was allowed to react with 2*N*-sulphuric acid for 15 minutes.

In a third experiment the compound of m. p. 153° (0·5 g.) was heated with 2*N*-sulphuric acid (25 ml.) on the steam-bath for one hour and the resulting deep-red insoluble resin digested with warm alcohol. The granular product was recrystallised from benzene, forming colourless prisms (80 mg.), m. p. 288—290°, identical with "2 : 3-dihydrocarbazole." Further extraction of the original aqueous solution gave only a trace of yellow gum.

Action of Hot Alcoholic Acetic Acid on 1 : 2 : 3 : 4-Tetrahydrocarbazolyl Hydroperoxide and on Compound, m. p. 153°.—When a solution of the peroxide (1·0 g.) in a mixture of alcohol (25 ml.) and acetic acid (20 ml.) was heated on the steam-bath for 10 minutes a colourless crystalline solid began to separate

from the dark red liquid. On isolation and washing with a little alcohol this compound (0·12 g.) had m. p. 293—295°, undepressed on admixture with "2 : 3-dihydrocarbazole," m. p. 293—295°. Evaporation of the dark filtrate followed by distillation of the residue in a high vacuum gave a yellow oil (0·22 g.), b. p. 160—180°/0·4 mm., which yielded only a small amount of a colourless solid, m. p. 236—238° (decomp.).

When the peroxide was replaced by the compound of m. p. 153° in the foregoing experiment the "dihydrocarbazole" (0·32 g.), m. p. 293—295°, separated and then distillation of the alcohol and acetic acid liquor left a gum from which a trace of the colourless compound, m. p. 236—238°, was obtained. The reaction mixture did not contain detectable amounts of *cyclo*pentane*spiro*-2-ϕ-indoxyl.

Catalytic Reduction of 1 : 2 : 3 : 4-*Tetrahydrocarbazolyl Hydroperoxide.*—Reduction of the hydroperoxide (0·95 g.) in methanol (50 ml.) with hydrogen and a palladium charcoal catalyst gave a good yield of 1 : 2 : 3 : 4-tetrahydrocarbazole, m. p. and mixed m. p. 117—118°.

A solution of the peroxide (1 g.) in methanol (70 ml.) containing Adams's platinum catalyst (0·1 g.) was agitated with hydrogen for 1½ hours. On isolation the product slowly solidified and, after being washed with a little ether, was recrystallised from the same solvent, giving the *hydroxyhexahydrocarbazole* in colourless needles, m. p. 104—105°, which in contact with the mother-liquor slowly changed to colourless prisms (0·68 g.), m. p. 110° (Found: C, 76·1; H, 8·3; N, 7·1. $C_{12}H_{15}ON$ requires C, 76·2; H, 7·9; N, 7·4%). Recrystallisation of the prismatic form from ether and seeding with the needle form gave the compound as a mixture of needles and prisms which on being kept changed completely into the prismatic form. This product is slightly soluble in light petroleum, moderately soluble in benzene, and readily soluble in methanol or alcohol. On treatment with dilute hydrochloric acid the compound was dehydrated, giving 1 : 2 : 3 : 4-tetrahydrocarbazole.

Reduction of the compound, m. p. 153°, with Adams's catalyst gave rise to the same hydroxyhexahydrocarbazole, m. p. 109—110°.

Derivatives of cyclo*Pentane*spiro-2-ϕ-*indoxyl* (VI).—Specimens of this compound prepared by the methods of Perkin and Plant (*J.*, 1923, **123**, 689) and Plant and Tomlinson (*J.*, 1933, 295) were readily oximated in pyridine, giving the *oxime* which formed pale yellow, rectangular prisms, m. p. 158°, from aqueous methanol (Found: N, 14·1. $C_{12}H_{14}ON_2$ requires N, 13·9%). The *oxime* of the *N*-acetyl derivative of the ϕ-indoxyl was prepared by the same method and separated from benzene–light petroleum (b. p. 60—80°) in colourless irregular prisms, m. p. 168° (Found: N, 11·5. $C_{14}H_{16}O_2N_2$ requires N, 11·5%).

Hydrogenation of the ϕ-indoxyl (1·22 g.) in methanol (50 ml.) with hydrogen and a platinum catalyst during 9 hours gave rise to a greenish-brown oil which partly crystallised and was repeatedly extracted with boiling light petroleum (b. p. 60—80°) to remove unchanged material. Crystallised from ethyl acetate, the residue (0·72 g.) gave *cyclo*pentane*spiro*-2-(4 : 5 : 6 : 7-tetrahydro-ϕ-indoxyl) (XIII) in very pale green rods, m. p. 190° (Found: C, 75·2; H, 8·8. Calc. for $C_{12}H_{17}ON$: C, 75·4; H, 8·9%) (cf. Witkop, *loc. cit.*, who gives m. p. 193°). This compound readily dissolved in dilute mineral acids and behaved with nitrous acid as a secondary amine. It sublimed unchanged at 160—165°/0·03 mm.

In an attempt to crystallise this tetrahydro-derivative from benzene the compound absorbed oxygen giving a *peroxide* which separated in colourless prisms, m. p. 125° (decomp.) (Found: C, 64·7; H, 7·7; N, 6·4. $C_{12}H_{17}O_2N$ requires C, 64·6; H, 7·6; N, 6·3%). This compound, which was much less soluble in benzene than the parent tetrahydro-ϕ-indoxyl, readily dissolved in dilute mineral acids, and liberated iodine from acidified aqueous potassium iodide.

1-*Hydroxy*-1 : 2 : 3 : 4-*tetrahydrocarbazole* (XVII).—1-Keto-1 : 2 : 3 : 4-tetrahydrocarbazole (Kent, *J.*, 1935, 976) (1·95 g.) in ether (220 ml.) was gradually added to a solution of lithium aluminium hydride (0·40 g.) in ether (75 ml.). Ten minutes later ice-cold water (20 ml.) was added, followed by 10% sulphuric acid (10 ml.). The resulting crude 1-hydroxy-1 : 2 : 3 : 4-tetrahydrocarbazole (1·64 g.), m. p. 82—100°, isolated with ether and recrystallised from acetone–light petroleum (b. p. 60—80°), formed colourless rectangular tablets, m. p. 115°, identical with a specimen of so-called "11-hydroxy-2 : 3 : 4 : 11-tetrahydrocarbazole," m. p. 115° (Plant and Tomlinson, *J.*, 1931, 3324) (Found: C, 77·1; H, 6·7; N, 7·55. Calc. for $C_{12}H_{13}ON$: C, 77·0; H, 6·95; N, 7·5%).

The authors express their gratitude to Professor R. A. Morton, of the Biochemistry Department, for kindly providing facilities for the measurement of the ultra-violet absorption spectra recorded and for discussing the interpretation of these, and also to Mr. C. A. McDowell for his interest in this work.

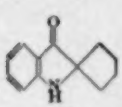
UNIVERSITY OF LIVERPOOL. [*Received, April 5th*, 1950.]

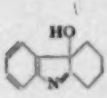
437. *The Structure of Certain Compounds derived from Tetrahydrocarbazole.*

By S. G. P. Plant and Muriel L. Tomlinson.

The substance obtained from the product of bromination of certain acyltetrahydrocarbazoles (*J.*, 1931, 3324), and previously thought to be 11-hydroxy-2 : 3 : 4 : 11-tetrahydrocarbazole, has been shown to be 1-hydroxy-1 : 2 : 3 : 4-tetrahydrocarbazole, while an isomeric compound obtained from the bromination of 1 : 2 : 3 : 4-tetrahydrocarbazole itself (*J.*, 1933, 298), and regarded as 10-hydroxy-1 : 2 : 3 : 10-tetrahydrocarbazole, is 11-hydroxytetrahydrocarbazolenine. Both isomers gave, on dehydration, a substance originally thought to be 2 : 3-dihydrocarbazole, but which is, in fact, 1 : 2 : 3 : 4 : 1′ : 2′ : 3′ : 4′-octahydro-1 : 9-9′ : 1′-dicarbazolylene, as shown by dehydrogenation and determination of molecular weight.

It has recently been shown (Plant and Robinson, *Nature*, 1950, **165**, 36) that it is necessary to revise the structures previously assigned to two isomeric compounds, $C_{13}H_{13}ON$, derived from tetrahydrocarbazole and regarded as *cyclo*pentane*spiro*-2-ϕ-indoxyl (I) and 11-hydroxytetrahydrocarbazolenine (II) respectively. The same conclusions were reached independently by


(I.)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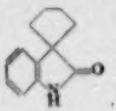
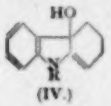

(III.)

Witkop (*J. Amer. Chem. Soc.*, 1950, **72**, 614), and conclusive evidence has been adduced that the former is *cyclo*pentane*spiro*oxindole (III) and the latter authentic *cyclo*pentane*spiro*-2-ϕ-indoxyl (I). It has been realised for some time that revision must be made of the structures assigned to two other isomeric compounds of the composition $C_{13}H_{13}ON$, and their derivatives, also obtained from tetrahydrocarbazole (see Plant, Robinson, and Tomlinson, *Nature*, 1950, **165**, 928), and investigations into some of the problems involved are in progress. A recent communication by Patrick and Witkop (*J. Amer. Chem. Soc.*, 1950, **72**, 633) in which reference is made to certain of these compounds makes it desirable to record some of our experimental results at this stage.

When 9-benzoyl(and 9-cinnamoyl)-tetrahydrocarbazole were treated with bromine in acetic acid, and the solutions immediately poured into water, compounds described as 11-hydroxy-9-benzoyl(or -cinnamoyl)-2 : 3 : 4 : 11-tetrahydrocarbazole (IV; R = Bz or CHPh:CH·CO) were obtained (*J.*, 1931, 3324). They were hydrolysed and subsequently benzoyl-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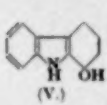
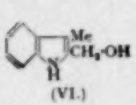

(V.)

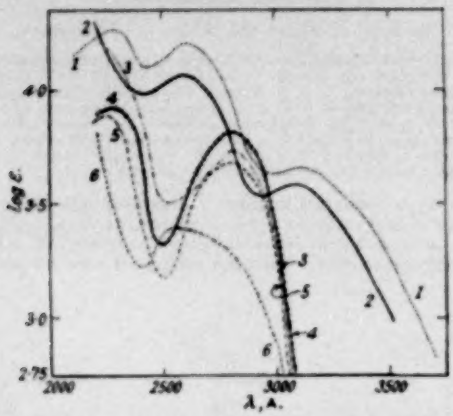

(VI.)

ated to the so-called 11-hydroxy- (IV; R = H) and 11-benzoyloxy-2 : 3 : 4 : 11-tetrahydrocarbazole. The possibility has existed that these substances are 1-hydroxy-1 : 2 : 3 : 4-tetrahydrocarbazole (V) and the corresponding acyl derivatives, and, in fact, an analogous compound obtained from 1-acetyl-2 : 3-dimethylindole was regarded as 3-methyl-2-hydroxymethylindole (VI) rather than the isomeric (VII) (*J.*, 1933, 955) (in this connection see Taylor, *Helv. Chim. Acta*, 1950, **33**, 164). The correctness of the alternative formulation has now been established by the preparation of (V), together with 1-hydroxyhexahydrocarbazole, by the reduction of 1-ketotetrahydrocarbazole with sodium and boiling alcohol. Ultra-violet light absorption spectra of the substances 1-hydroxy-9-benzoyl-, 9-benzoyl-, 1-hydroxy-, and 1-benzoyloxy-tetrahydrocarbazole (Fig. 1) in methanol confirm that they are all of the type represented by (V) and are evidence against the possibility that the first is (IV; R = Bz) and undergoes the requisite structural change on hydrolysis.

A different compound, $C_{13}H_{13}ON$, has been obtained by the bromination of tetrahydrocarbazole under similar conditions, and this was first formulated as (VIII) (*J.*, 1933, 298). It has now been found that the dye obtained from it by diazotisation and coupling with β-naphthol has the composition $C_{23}H_{16}O_2N_2$ (Found : C, 72·9; H, 5·7; N, 7·9. Required : C, 73·3; H, 5·55;

FIG. 1.

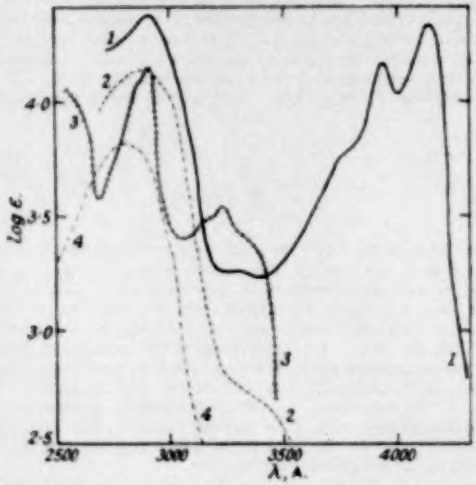
Ultra-violet absorption spectra.



1, 9-*Benzoyl*-1 : 2 : 3 : 4-*tetrahydrocarbazole*. 2, 1-*Hydroxy*-9-*benzoyl*-1 : 2 : 3 : 4-*tetrahydrocarbazole*. 3, 1-*Benzoyloxy*-1 : 2 : 3 : 4-*tetrahydrocarbazole*. 4, 1 : 2 : 3 : 4-*Tetrahydrocarbazole*. 5, 1-*Hydroxy*-1 : 2 : 3 : 4-*tetrahydrocarbazole*. 6, 11-*Hydroxytetrahydrocarbazolenine*. (*All determined in methanol solution.*)

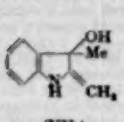
FIG. 2.

Ultra-violet absorption spectra.

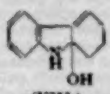


1, 1 : 9-9′ : 1′-*Dicarbazolylene*. 2, 1 : 2 : 3 : 4 : 1′ : 2′ : 3′ : 4′-*Octahydro*-1 : 9-9′ : 1′-*dicarbazolylene*. (1 *and* 2 *in dioxan solution.*) 3, *Carbazole*. 4, 1 : 2 : 3 : 4-*Tetrahydrocarbazole*. (3 *and* 4 *in methanol solution.*)

N, 7·8%), and not $C_{12}H_{11}O_2N_3$, and the substance is the authentic 11-hydroxytetrahydrocarbazolenine (II) as also stated by Patrick and Witkop (*loc. cit.*).



(VII.)



(VIII.)

(IX.)

(X.)

The compound obtained from both 1-hydroxytetrahydrocarbazole and 11-hydroxytetrahydrocarbazolenine by dehydration with boiling acetic anhydride and in other ways (*J.*, 1931, 3324; 1933, 298), and previously called "2 : 3-dihydrocarbazole," is evidently 1 : 2 : 3 : 4 : 1′ : 2′ : 3′ : 4′-octahydro-1 : 9-9′ : 1′-dicarbazolylene (IX). This follows not only from its molecular weight but from the fact that the product of dehydrogenation with sulphur in boiling quinoline (Tomlinson, D.Phil. Thesis, Oxford, 1933) was not carbazole, but a substance of the composition $C_{24}H_{14}N_2$, which must be 1 : 9-9′ : 1′-dicarbazolylene (X). The formulations (IX) and (X) are supported by ultra-violet absorption spectra (Fig. 2).

Experimental.

1-*Hydroxy*-1 : 2 : 3 : 4-*tetrahydrocarbazole* [with B. P. Moore].—Sodium (6 g.) was added in portions to a boiling solution of 1-keto-1 : 2 : 3 : 4-tetrahydrocarbazole (2 g.) in absolute (Mg-dried) ethanol (80 c.c.) under reflux. After the mixture had been poured into water and the product extracted with ether, the extract was washed with water, dried (Na_2SO_4), and concentrated to small bulk (9 c.c.). When this was cooled below 0°, 1-*hydroxy*-1 : 2 : 3 : 4 : 10 : 11-*hexahydrocarbazole* (0·5 g., soluble in dilute mineral acids), colourless plates, m. p. 140° (from ethanol), separated (Found: C, 76·6; H, 7·9. $C_{12}H_{13}ON$ requires C, 76·2; H, 7·9%). Benzoylation with benzoyl chloride and sodium hydroxide gave a monobenzoyl compound, colourless needles, m. p. 136—137° [from light petroleum (b. p. 60—80°)], evidently 1-*hydroxy*-9-*benzoyl*-1 : 2 : 3 : 4 : 10 : 11-*hexahydrocarbazole* since it is insoluble in dilute hydrochloric acid (Found: C, 77·8; H, 6·2. $C_{19}H_{17}O_2N$ requires C, 77·8; H, 6·5%). After the above basic product had been removed, the solution was gradually diluted with light petroleum (b. p. 60—80°) in order to effect the separation of a small quantity (about 0·2 g.) of unchanged ketotetrahydrocarbazole. This was removed by filtration, the solution evaporated, the yellow gummy residue dissolved in a little warm benzene, and the mixture treated drop-wise with light petroleum (b. p. 60—80°) until crystallisation started, and cooled below 0°. 1-Hydroxy-1 : 2 : 3 : 4-tetrahydrocarbazole (0·2 g.) then separated in colourless prisms, m. p. 112—115°, identical (mixed m. p.) with a specimen of the substance obtained by Plant and Tomlinson (*J.*, 1931, 3324) from 9-benzoyltetrahydrocarbazole and previously regarded as 11-hydroxy-2 : 3 : 4 : 11-tetrahydrocarbazole. Both specimens gave, with concentrated sulphuric acid, a carmine colour which faded slowly when the solution was kept and rapidly when it was treated with nitric acid, and both gave a yellow solution in concentrated nitric acid. The use of 1-hydroxy-1 : 2 : 3 : 4-tetrahydrocarbazole in pharmacological tests is mentioned by Eddy (*J. Pharm. Exp. Ther.*, 1930, **65**, 308), and its m. p. is stated to be 118·5°, but no analysis or details of its preparation seem to have been published. In the absence of such information it is thought possible that the substance used by Eddy may have been tetrahydrocarbazole, m. p. 118°, which can be obtained by reduction of the keto-compound under certain conditions (see Mears, Oakeshott, and Plant, *J.*, 1934, 272).

1 : 2 : 3 : 4 : 1′ : 2′ : 3′ : 4′-*Octahydro*-1 : 9-9′ : 1′-*dicarbazolylene*.—(*a*) When 1-hydroxytetrahydrocarbazole (from 1-ketotetrahydrocarbazole) was boiled for 15 minutes with acetic anhydride, this compound separated in colourless prisms, m. p. 290—293°, identical (mixed m. p.) with the substance (previously regarded as 2 : 3-dihydrocarbazole) obtained by Plant and Tomlinson (*J.*, 1933, 298) from the product of bromination of tetrahydrocarbazole. This substance is not dissolved by dilute hydrochloric acid.

(*b*) A boiling solution of 1-ketotetrahydrocarbazole (3 g.) in commercial absolute alcohol (150 c.c.) was treated with sodium (9 g.), as much alcohol as possible was removed on a steam-bath under reduced pressure, and the residue was diluted with water and just acidified with acetic acid. The sticky precipitate was taken up in ether and, when the extract was dried ($CaCl_2$) and concentrated, a crystalline product (0·6 g.) separated. After this had been recrystallised from benzene, the octahydro-compound, m. p. 290—293°, was obtained. The true m. p. of the substance was determined by heating it rapidly in a capillary tube. When heated slowly it melted at 257—260° and partly resolidified as observed by Patrick and Witkop (*loc. cit.*). This phenomenon is evidently due to some dehydrogenation to the more aromatic compound described below, since the material which had been kept at 265° for some minutes dissolved in hot toluene to give the characteristic fluorescence and deposited solid, m. p. 320—325°, raised to 325—330° by admixture with the dehydrogenation product.

The molecular weight of the octahydro-compound was difficult to determine with accuracy by Rast's method owing to the small solubility of the substance in camphor, and values ranging between 274 and 344 were obtained, but these serve to establish the fact that the compound is derived from two tetrahydrocarbazole components ($C_{24}H_{22}N_2$ requires *M*, 338).

With concentrated sulphuric acid the octahydro-compound gave a faint brown colour which was changed to a deep orange-brown by a drop of nitric acid (tetrahydrocarbazole gives a colourless, changed

to faintly yellow, solution). When the compound was melted with oxalic acid a brown colour appeared (tetrahydrocarbazole gives a red colour).

1 : 9-9' : 1'-*Dicarbazolylene*.—A solution of the above octahydro-compound (0·6 g.) in quinoline (20 c.c.) to which sulphur (0·116 g.) had been added, was boiled for ½ hour, and poured into ice–dilute hydrochloric acid. The precipitate was dried and heated with iron filings under reduced pressure, and, when the crystalline sublimate had been extracted with hot toluene, the solution gave 1 : 9-9' : 1'-*dicarbazolylene*, on cooling, in greenish yellow needles, m. p. 337° (Found: C, 87·6; H, 4·5. $C_{36}H_{18}N_2$ requires C, 87·3; H, 4·2%). It showed a brilliant violet fluorescence in benzene or toluene. The same substance was obtained when the octahydro-compound was dehydrogenated with chloranil in boiling xylene (compare Barclay and Campbell, *J.*, 1945, 530), or heated with palladised charcoal in hydrogen. The compound gave a green colour, becoming violet, with concentrated sulphuric acid, changed to emerald green by nitric acid (carbazole: yellow, changed to intense green). The melt with oxalic acid was yellowish-green (carbazole gives a blue melt).

The authors are indebted to Professor Sir Robert Robinson, P.R.S., for his interest in this work and for much valuable discussion.

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438. *Thiophen Derivatives of Potential Biological Interest. Part I. Thiophen Analogues of Stilbene and of Related Compounds.*

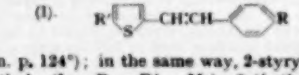
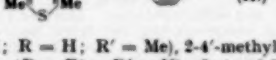
By NG. PH. BUU-HOÏ, NG. HOÁN, and DENISE LAVIT.

Several new derivatives of thiophen akin to stilbene and to αβ-diphenylacrylonitrile have been prepared by known methods for biological investigation. The properties of some aldehydes of the thiophen series have been examined, particularly the reaction with ethyl acetoacetate and the Ullmann acridine synthesis.

NUMEROUS investigations have concerned the influence, on biological activity, of the replacement of phenyl nuclei by thiophen groups in the molecules of various pharmacologically active substances (see Steinkopf, "Die Chemie des Thiophens," Dresden, 1941, p. 29; Buu-Hoï and Hoán, *Rec. Trav. chim.*, 1948, **67**, 309). The chief result has been to show that generally the thiophen nucleus is a less potent toxophore than the benzene nucleus. Some results of practical significance have been gathered in that respect, such as the recent discovery of Chlorothene and Bromothene, two substances of the pyribenzamine series which have greater antihistamine activity and lower toxicity than their benzene analogues (Lichtfield, Adams, Goddard, Jaeger, and Alonso, *Bull. Johns Hopkins Hosp.*, 1947, **81**, 55). Such facts are bringing renewed incentive to a broader investigation of series of thiophen compounds with potential biological interest. The present paper deals mainly with the preparation of substances akin to stilbene.

The aldehydes used as intermediates in this work were 2-formyl-, 2-formyl-5-methyl-, 5-chloro-2-formyl-, and 3-formyl-2 : 5-dimethyl-thiophen. These were readily prepared by a modification of King and Nord's method (*J. Org. Chem.*, 1948, **13**, 635) involving the use of phosphorus oxychloride and *N*-methylformanilide, which was much superior to the reaction of ethyl orthoformate with the appropriate thiophen Grignard reagents (Grischkewitsch-Trochimowski, *J. Russ. Phys. Chem. Soc.*, 1911, **43**, 204; 1912, **44**, 570) and to the more recent method of Emerson and Patrick (*J. Org. Chem.*, 1949, **14**, 790) based on the oxidation of primary thiophen alcohols.

Reaction of 2-formylthiophen with benzylmagnesium chloride, followed by dehydration of the secondary alcohol thus formed, gave as the main product a solid 2-styrylthiophen (I; R = R' = H) assumed to be the *trans*-form by reason of its high melting point (111°; *trans*-stilbene

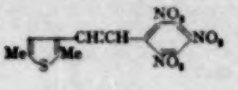
(I.)   (II.)

has m. p. 124°); in the same way, 2-styryl-5-methyl (I; R = H; R' = Me), 2-4'-methylstyryl-5-methyl- (I; R = R' = Me), 2-4'-ethylstyryl- (I; R = Et; R' = H), 3-styryl-2 : 5-dimethyl- (II; R = H) and 3-4'-methylstyryl-2 : 5-dimethyl-thiophen (II; R = Me) were obtained. In some cases, there were signs of the simultaneous formation of a second isomer (probably the *cis*-).

Another route to analogues of stilbene was the condensation of thiophen aldehydes with 2 : 4 : 6-trinitrotoluene in the presence of piperidine, according to a procedure used in the aro-

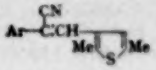
matic series by Pfeiffer and Monath (*Ber.*, 1906, **39**, 1306). The compounds (III; R = H, Me, and Cl) and (IV) were thus readily obtained. A third route was the condensation of thiophen

(III.)

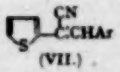
 (IV.)

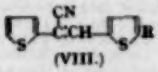
aldehydes in the presence of mineral or organic bases with arylacetonitriles. A series of α-aryl-β-2-thienylacrylonitriles (as V) and α-aryl-β-3-thienylacrylonitriles (as VI) was thus easily

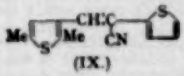
(V.)

 (VI.)

prepared and is listed in Table I. The analogous condensation of various aromatic aldehydes with 2-thienylacetonitrile yielded a series of β-aryl-α-2-thienylacrylonitriles of type (VII),

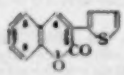

(VII.)

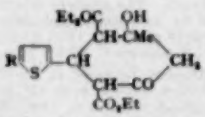

(VIII.)


(IX.)

listed in Table II. When thiophen aldehydes were used in the latter process, αβ-dithienylacrylonitriles of types (VIII) and (IX) were obtained (see Table II).

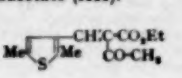
It is worth mention that although β-*p*-methoxyphenyl-α-2-thienylacrylonitrile (VII; Ar = (*p*-MeO·C$_6$H$_4$) was readily demethylated by pyridine hydrochloride, the isomeric nitrile (VII; Ar = *o*-MeO·C$_6$H$_4$) was completely converted into 3-2′-thienylcoumarin (X). This abnormal behaviour was also found in the aromatic series, 1-phenyl-2-*o*-methoxyphenylacrylonitrile being similarly transformed into 3-phenylcoumarin by heating it for a short time with pyridine hydrochloride.

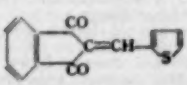
(X.) 

 (XI.)

The ready accessibility of thiophen aldehydes by the *N*-formanilide method led us to investigate their properties further. When 2-formylthiophen and ethyl acetoacetate in equimolecular amounts were treated with a few drops of piperidine, the expected ethyl 2-thienylideneacetoacetate was not formed, but instead ethyl 4-hydroxy-6-keto-2-2′-thienyl-4-methyl*cyclo*hexan-1 : 3-dicarboxylate (XI; R = H) was obtained; similarly, the 5-chloro-2-thienyl compound (XI; R = Cl) was formed from an equimolecular mixture of 5-chloro-2-formylthiophen, ethyl acetoacetate, and piperidine. Both compounds (XI) were of course obtained when one molecule of aldehyde was allowed to react with two molecules of ethyl acetoacetate.

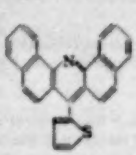
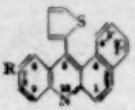
It may be recalled that, in the benzene series, ethyl benzylideneacetoacetate was readily obtained when equimolecular amounts of benzaldehyde and ethyl acetoacetate were treated with piperidine (Knoevenagel, *Ber.*, 1896, **29**, 172), and we found that *p*-chlorobenzaldehyde behaved similarly. An unexpected result was therefore recorded with 3-formyl-2 : 5-dimethylthiophen, which behaved like an aromatic aldehyde, and yielded ethyl (2 : 5-dimethyl-3-thienylidene)acetoacetate (XII).

(XII.) 

 (XIII.)

In some other reactions, 2-formylthiophen behaved like benzaldehyde, yielding, for instance, the 2-thienylidene derivative (XIII) with indane-1 : 3-dione, and with an equimolecular mixture of α-naphthol and α-naphthylamine 5-2′-thienyl-1 : 2 : 8 : 9-dibenzacridine (XIV) (cf. the synthesis of 5-phenyl-1 : 2 : 8 : 9-dibenzacridine by Senier and Austin, *J.*, 1906, **89**, 1395).

Extensions of this acridine synthesis were the ready preparation of 5-2′-thienyl- (XV; R = H) and 5-2′-thienyl-7-methyl-3 : 4-benzacridine (XV; R = Me).

(XIV.)   (XV.)

Many of our new compounds are under biological investigation in this Institute by Professor A. Lacassagne, in particular 2-(*p*-dimethylaminophenyl)-1-2′-thienylacrylonitrile, which is isosteric with the carcinogenic 1-phenyl-2-(*p*-dimethylaminophenyl)acrylonitrile.

Experimental.

Preparation of 2-Formylthiophen and its Homologues.—The following modification of the King–Nord procedure (*loc. cit.*) was used throughout. To a mixture of thiophen (84 g.) and *N*-methylformanilide (180 g.), in a flask fitted with a reflux condenser and a mechanical stirrer, phosphorus oxychloride (192 g.) was added; reaction set in immediately and the liquid boiled. The reaction subsided after about 30 minutes, and the mixture was then refluxed for 1 hour on a water-bath. After cooling, it was treated with sodium acetate (300 g.) in water (500 c.c.) and steam-distilled. 2-Formylthiophen was extracted from the distillate with ether, with dilute hydrochloric acid, then with dilute aqueous sodium carbonate, dried (Na_2SO_4), and freed from solvent, and the residue was distilled *in vacuo*. The yields were generally superior by 10—15 g. to those recorded by King and Nord. The aldehyde had b. p. 93—94°/20 mm.

5-Chloro-2-formyl-, b. p. 103—105°/13 mm., and 2-formyl-5-methyl-thiophen, b. p. 107°/13 mm., were prepared similarly, with the same yields. The condensation of 2 : 5-dimethylthiophen to give 3-formyl-2 : 5-dimethylthiophen, b. p. 115°/13 mm., was less easy and required 2 hours' refluxing to afford good yields, probably because of the lower reactivity at the 3-position.

2-Styrylthiophen and its Analogues.—A solution of 2-formylthiophen (5 g.) in anhydrous ether (10 c.c.) was added in small portions to a cooled Grignard solution [from magnesium (1·3 g.) and benzyl chloride (6·8 g.) in ether (50 c.c.)]. After 15 minutes' refluxing, the reaction product was poured into 10% aqueous sulphuric acid, and the crude carbinol from the ethereal layer was refluxed for 5 minutes with 98% formic acid (20 c.c.). The mixture was poured into water, and the *styryl* compound taken up in benzene and purified by vacuum-fractionation (b. p. 170—180°/13 mm.). It formed, from ethanol, light colourless leaflets (5 g.), m. p. 111°, giving an orange-red colour with sulphuric acid (Found: C, 77·2; H, 5·4. $C_{12}H_{10}S$ requires C, 77·4; H, 5·4%).

2-Styryl-5-methylthiophen, prepared in the same way, had b. p. 185—190°/13 mm. and crystallised from ethanol in colourless leaflets m. p. 85°, giving a bright red colour with sulphuric acid (Found: C, 78·0; H, 6·2. $C_{13}H_{12}S$ requires C, 78·0; H, 6·0%). *2-4′-Methylstyryl-5-methylthiophen* had b. p. 185—195°/13 mm. and formed from ethanol glistening colourless leaflets, m. p. 94° (Found: C, 78·3; H, 6·6. $C_{14}H_{14}S$ requires C, 78·5; H, 6·5%). The isosteric 4 : 4′-dimethylstilbene (Anschütz and Wirtz, *Ber.*, 1885, **18**, 1948) has m. p. 179° and b. p. 304—305°. *2-4′-Ethylstyrylthiophen* was a pale yellow oil, b. p. 190—195°/13 mm., giving an orange-red colour with sulphuric acid (Found: C, 78·3; H, 6·6. $C_{14}H_{14}S$ requires C, 78·5; H, 6·5%). *3-Styryl-2 : 5-dimethylthiophen* had b. p. 195—205°/13 mm. and formed from ethanol colourless needles, m. p. 55°, giving with sulphuric acid a deep orange-red colour (Found: C, 78·5; H, 6·9. $C_{14}H_{14}S$ requires C, 78·5; H, 6·5%). *3-4′-Methylstyryl-2 : 5-dimethylthiophen* formed from ethanol colourless leaflets, m. p. 101°, b. p. 200—210°/13 mm., giving a crimson-red colour with sulphuric acid (Found: C, 78·6; H, 7·0. $C_{15}H_{16}S$ requires C, 78·9; H, 7·0%). Crystallisation of the mother-liquors of all the foregoing solid compounds yielded small amounts of oily, sulphur-containing substances which have approximately the same b. p. as the crystals and which are stereoisomers thereof.

2-2′-Thienylideneindane-1 : 3-dione (XIII).—One drop of piperidine was added to a stirred mixture of indane-1 : 3-dione (1 g.) and 2-formylthiophen (0·9 g.) in ethanol (10 c.c.). An exothermic reaction at once set in. The *thienylidene* derivative formed was collected, washed with methanol, and recrystallised from ethanol in long golden-yellow needles, m. p. 177°, giving an orange-red colour with sulphuric acid (Found: C, 69·8; H, 3·5. $C_{14}H_8O_2S$ requires C, 70·0; H, 3·3%).

5-2′-Thienyl-1 : 2 : 8 : 9-dibenzacridine (XIV).—To a boiling mixture of α-naphthylamine (7 g.) and α-naphthol (7 g.), 2-formylthiophen (5·5 g.) was added drop-wise with stirring. Boiling was then continued for 5 minutes, and the reaction product distilled in a high vacuum; crystallisation from benzene of the resin, b. p. >280°/2 mm., gave yellow prisms, m. p. 224° (yield, 40%), producing an orange-yellow colour with sulphuric acid (Found: N, 3·6. $C_{21}H_{13}NS$ requires N, 3·9%). The picrate formed yellow prisms, m. p. 236—237° (decomp.), from xylene.

5-2′-Thienyl-3 : 4-benzacridine.—Similarly prepared by addition of 2-formylthiophen (5·5 g.) to a boiling mixture of β-naphthol (7 g.) and aniline (4·8 g.), this *base* crystallised from ethanol in fine pale yellow prisms, m. p. 191° (Found: N, 4·2. $C_{21}H_{13}NS$ requires N, 4·5%), giving a picrate, fine yellow needles, m. p. 235—236° (decomp.) (Buu-Hoï and Hoán, *Rec. Trav. chim.*, 1949, **68**, 5, gave m. p. 237°). *5-2′-Thienyl-7-methyl-3 : 4-benzacridine* (from the same aldehyde, β-naphthol, and *p*-toluidine) formed

from ethanol pale yellow needles, m. p. 237° (sublimation above 210°) (Found: N, 4·2. $C_{20}H_{12}NS$ requires N, 4·3%), giving a picrate, m. p. *ca.* 245° (decomp.).

2-(2 : 4 : 6-*Trinitrostyryl*)*thiophen and its Analogues.*—A solution of 2 : 4 : 6-trinitrotoluene (1 g.) and 2-formylthiophen (0·5 g.) in dry benzene (10 c.c.) was gently refluxed for 3 hours with 2 drops of piperidine; the solvent was distilled off, and the residue recrystallised twice from ethanol, giving glistening dark yellow elongated prisms, m. p. 140° (1·2 g.); sulphuric acid produced an orange colour. This compound has recently been described by Emerson and Patrick (*loc. cit.*).

2-(2 : 4 : 6-*Trinitrostyryl*)-5-*methylthiophen*, similarly prepared from 2-formyl-5-methylthiophen, formed from ethanol reddish-yellow needles, m. p. 164—165° (Found: N, 12·2. $C_{13}H_9O_6N_3S$ requires N, 12·5%). 5-*Chloro*-1-(2 : 4 : 6-*trinitrostyryl*)*thiophen* formed from ethanol brownish-yellow needles, m. p. 150°, giving a brown colour with sulphuric acid (Found: N, 11·6. $C_{12}H_6O_6N_3ClS$ requires N, 11·8%). 3-(2 : 4 : 6-*Trinitrostyryl*)-2 : 5-*dimethylthiophen* (24 hours' heating) formed from ethanol long red needles, m. p. 175°, giving a brownish-yellow colour with sulphuric acid (Found: N, 11·9. $C_{14}H_{11}O_6N_3S$ requires N, 12·0%).

Ethyl 4-*Hydroxy*-6-*keto*-2-2′-*thienyl*-4-*methylcyclohexane*-1 : 3-*dicarboxylate.*—An equimolecular mixture of 2-formylthiophen (8 g.) and ethyl acetoacetate (10 g.) was cooled in ice, and 8 drops of piperidine were stirred in. After 12 hours at room temperature, the cyclic *ester*, which had solidified, was filtered off and recrystallised twice from ether; fine colourless needles, m. p. 106°, were obtained, giving an orange-yellow colour with sulphuric acid (Found: C, 57·6; H, 6·3. $C_{17}H_{20}O_5S$ requires C, 57·6; H, 6·2%). The same compound was obtained in almost quantitative yield when the proportion of ethyl acetoacetate was doubled, and the mixture kept for 48 hours.

The 5-*chloro*-2-*thienyl* analogue crystallised from ether in glistening colourless needles, m. p. 150°, giving with sulphuric acid a yellow colour (Found: C, 52·4; H, 5·5. $C_{17}H_{19}O_5ClS$ requires C, 52·4; H, 5·4%).

Ethyl p-*Chlorobenzylideneacetoacetate.*—A mixture of *p*-chlorobenzaldehyde (5 g.), ethyl acetoacetate (4·6 g.), and piperidine (4 drops) was kept at room temperature for 24 hours; the *ester* obtained crystallised from ether in long colourless needles (8 g.), m. p. 87°, giving with sulphuric acid a yellow colour (Found: C, 61·5; H, 5·2. $C_{13}H_{13}O_3Cl$ requires C, 61·7; H, 5·1%).

Ethyl (2 : 5-*Dimethyl*-3-*thienylidene*)*acetoacetate.*—Obtained from 3-formyl-2 : 5-dimethylthiophen (2·6 g.), ethyl acetoacetate (2·3 g.), and piperidine (2 drops) (24 hours at room temperature), this *compound* formed from ether colourless prisms (4 g.), m. p. 72°, giving with sulphuric acid an orange-red colour (Found: C, 61·6; H, 6·5. $C_{14}H_{18}O_3S$ requires C, 61·9; H, 6·3%).

TABLE I.

Acrylonitriles of types (V) *and* (VI).

Acrylonitrile.[a]	M. p. (b. p.).	Formula.	Found, %. C.	Found, %. H.	Reqd., %. C.	Reqd., %. H.
α-*Phenyl*-β-2-*thienyl*-	90° (200—210°/13 mm.)	$C_{13}H_9NS$	73·6	4·6	73·9	4·3
α-*Phenyl*-β-(5-*methyl*-2-*thienyl*)-	83 (210—220°/13 mm.)	$C_{14}H_{11}NS$	74·5	5·0	74·7	4·9
α-*Phenyl*-β-(5-*chloro*-2-*thienyl*)-[b]	149	$C_{13}H_8NClS$	63·1	3·5	63·4	3·3
α-*Phenyl*-β-(2 : 5-*dimethyl*-3-*thienyl*)-	85	$C_{16}H_{15}NS$	75·2	5·6	75·3	5·4
α-p-*Tolyl*-β-2-*thienyl*-	118	$C_{14}H_{11}NS$	74·4	5·1	74·7	4·9
α-p-*Tolyl*-β-(5-*methyl*-2-*thienyl*)-	110	$C_{15}H_{13}NS$	75·1	5·4	75·3	5·4
α-p-*Tolyl*-β-(2 : 5-*dimethyl*-3-*thienyl*)-	91	$C_{16}H_{15}NS$	75·6	5·9	75·9	5·9
α-p-*Tolyl*-β-(5-*chloro*-2-*thienyl*)-[b]	154	$C_{14}H_{10}NClS$	64·4	3·9	64·6	3·8
α-1-*Naphthyl*-β-2-*thienyl*-[c]	97 (270—275°/13 mm.)	$C_{17}H_{11}NS$	78·1	4·4	78·2	4·2
α-1-*Naphthyl*-β-(5-*methyl*-2-*thienyl*)-[d]	145	$C_{18}H_{13}NS$	78·5	4·8	78·5	4·7
α-1-*Naphthyl*-β-(2 : 5-*dimethyl*-3-*thienyl*)-	76	$C_{19}H_{15}NS$	75·2	5·3	75·4	5·2
α-1-*Naphthyl*-β-(5-*chloro*-2-*thienyl*)-	152	$C_{17}H_{10}NClS$	68·8	3·6	68·9	3·4
α-p-*Nitrophenyl*-β-2-*thienyl*-	204	$C_{13}H_8O_2N_2S$	60·0	3·2	60·1	3·1
α-p-*Nitrophenyl*-β-(5-*methyl*-2-*thienyl*)-[c]	227 (subl. >200°)	$C_{14}H_{10}O_2N_2S$	62·1	3·9	62·2	3·7
α-p-*Nitrophenyl*-β-(2 : 5-*dimethyl*-3-*thienyl*)-	188	$C_{15}H_{12}O_2N_2S$	63·1	4·2	63·4	4·2
α-p-*Nitrophenyl*-β-(5-*chloro*-2-*thienyl*)-[b]	234 (subl.)	$C_{13}H_7O_2N_2SCl$	53·5	2·6	53·6	2·4
α-p-*Methoxyphenyl*-β-2-*thienyl*-	77	$C_{14}H_{11}ONS$	69·8	4·4	69·7	4·4
α-p-*Methoxyphenyl*-β-(5-*methyl*-2-*thienyl*)-	88	$C_{15}H_{13}ONS$	70·4	5·3	70·6	5·1
α-p-*Methoxyphenyl*-β-(5-*chloro*-2-*thienyl*)-	134	$C_{14}H_{10}ONSCl$	60·8	3·6	60·9	3·6
α-p-*Methoxyphenyl*-β-(2 : 5-*dimethyl*-3-*thienyl*)-	96	$C_{16}H_{15}ONS$	71·2	5·6	71·4	5·6
α-p-*Hydroxyphenyl*-β-2-*thienyl*-[c]	166	$C_{13}H_9ONS$	68·6	4·0	68·7	3·9
α-p-*Hydroxyphenyl*-β-(5-*methyl*-2-*thienyl*)-	208	$C_{14}H_{11}ONS$	69·8	4·8	69·7	4·6
α-p-*Hydroxyphenyl*-β-(5-*chloro*-2-*thienyl*)-	206	$C_{13}H_8ONSCl$	59·3	3·2	59·5	3·1
α-p-*Hydroxyphenyl*-β-(2 : 5-*dimethyl*-3-*thienyl*)-	187	$C_{15}H_{15}ONS$	70·3	5·1	70·6	5·0

[a] All yellow needles, unless otherwise stated. [b] Leaflets. [c] Prisms. [d] Orange.

TABLE II.

Acrylonitriles [a] of types (VII), (VIII), *and* (IX).

α-(2-Thienyl)acrylonitriles. [b]	M. p.	Formula.	Found, %. C.	Found, %. H.	Reqd., %. C.	Reqd., %. H.
β-2-*Furyl*- [c]	80°	$C_{11}H_7ONS$	65·6	3·8	65·7	3·5
β-(p-*Dimethylaminophenyl*)- [d]	160	$C_{15}H_{14}N_2S$	70·1	5·7	70·1	5·6
β-p-*Chlorophenyl*-	90	$C_{12}H_8NSCl$	63·2	3·5	63·4	3·3
β-p-*Methoxyphenyl*-	74	$C_{14}H_{11}ONS$	69·6	4·8	69·7	4·6
β-(3 : 4-*Dimethoxyphenyl*)- [e]	86	$C_{15}H_{13}O_2NS$	66·3	4·9	66·4	4·8
β-(3 : 4-*Methylenedioxyphenyl*)- [c]	106	$C_{14}H_9O_2NS$	65·6	3·7	65·9	3·5
β-o-*Methoxyphenyl*-	81 [e]	$C_{14}H_{11}ONS$	69·4	4·6	69·7	4·6
β-(5-*Methyl*-2-*thienyl*)- [c]	87	$C_{12}H_9NS_2$	62·2	3·8	62·3	3·9
β-(2 : 5-*Dimethyl*-3-*thienyl*)- [d]	105	$C_{13}H_{11}NS_2$	63·7	4·8	63·7	4·5
β-(5-*Chloro*-2-*thienyl*)-	115	$C_{11}H_6NS_2Cl$	52·3	2·6	52·4	2·4
β-p-*Hydroxyphenyl*-	176	$C_{13}H_9ONS$	68·5	4·1	68·7	4·0
β-(3 : 4-*Dihydroxyphenyl*)-	179—181	$C_{13}H_9O_2NS$	64·0	3·8	64·2	3·7

[a] Acrylonitriles of type (VIII) are functional derivatives of 1 : 2-di-2′-thienylethylene (Nahke, *Ber.*, 1897, **30**, 2041). [b] Yellow needles unless otherwise stated. [c] Prisms. [d] Leaflets. [e] B. p. 230—240°/13 mm.

Preparation of Acrylonitriles of Types (V), (VI), (VIII), and (IX).—These were prepared in the usual way by shaking the aldehyde and arylacetonitrile in warm ethanol, with a few drops of 30% aqueous potassium hydroxide. In most instances, there was an almost immediate separation of an oil which solidified when kept. The substance was collected, washed with water, and recrystallised from ethanol. In the case of *p*-nitrophenylacetonitrile, piperidine was used instead of potassium hydroxide, and the reaction was effected by 3 hours' boiling. 2-Thienylacetonitrile was condensed with aldehydes in the same way; it was prepared from 2-chloromethylthiophen (Blicke and Burchkalter, *J. Amer. Chem. Soc.*, 1942, **64**, 477) by Blicke and Zienty's method (*J. Amer. Chem. Soc.*, 1941, **63**, 2945). The products are recorded in Tables I and II. All these compounds give brown, red, or violet colours in sulphuric acid.

Demethylation of Acrylonitriles bearing Methoxy-groups.—This was effected by refluxing for 15 minutes a mixture of the required methoxy-compound (1 part) with redistilled pyridine hydrochloride. After dilution of the mixture with water, the precipitate formed was collected, washed thoroughly with water, dried, and crystallised from benzene; the yields were almost quantitative.

3-2′-*Thienylcoumarin* (X).—Demethylation of *β*-o-methoxyphenyl-α-2-thienylacrylonitrile (1·5 g.) with pyridine hydrochloride in the foregoing way, and crystallization of the reaction product from ethanol, yielded 3-2′-*thienylcoumarin* as pale yellow, fluffy needles (1·3 g.), m. p. 167°, giving a red colour with sulphuric acid (Found: C, 68·4; H, 2·8; N, 0. $C_{13}H_8O_2S$ requires C, 68·4; H, 3·5%). This compound was insoluble in dilute aqueous sodium hydroxide solutions in the cold.

1-*Phenyl*-2-o-*methoxyphenylacrylonitrile*, prepared from o-methoxybenzaldehyde and phenylacetonitrile, formed, from ethanol, silky, pale yellow needles, m. p. 46°, b. p. 222°/13 mm. (Found: N, 6·0. $C_{16}H_{13}ON$ requires N, 6·2%). On treatment with pyridine hydrochloride as above, it gave a quantitative yield of 3-phenylcoumarin, m. p. 140° (Oglialoro, *Ber.*, 1879, **12**, 2367).

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439. *The Conversion of Carbamates into Dithiocarbamates.*

By D. O. HOLLAND.

Carbon disulphide reacts with carbamylmethylammonium carbamylmethylcarbamate (II) at room temperature in aqueous alcohol to yield the corresponding dithiocarbamic derivative (I). Benzylammonium benzylcarbamate similarly yields benzylammonium benzyldithiocarbamate.

DURING an investigation of the preparation of carbamylmethylammonium carbamylmethyldithiocarbamate (I) (Cook, Heilbron, and Levy, *J.*, 1948, 201) by treating salts of aminoacetamide with bases and carbon disulphide, attempts were made to use sodium hydrogen carbonate as the base. By analogy with the compound formed by 2-aminooctanoamide hydrochloride under similar conditions (Erlenmeyer and Sigel, *Annalen*, 1875, **177**, 130) the reaction would have been expected to yield the carbamate (II). In fact, it was possible, by repeated extraction of the reaction mixture with alcohol (95%) and acetone and treatment of each extract with carbon disulphide, to obtain successive small quantities of the dithiocarbamate (I).

$CH_2{\cdot}CO{\cdot}NH_2$
$NH{\cdot}CS_2H{\cdot}NH_2{\cdot}CH_2{\cdot}CO{\cdot}NH_2$
(I.)

$CH_2{\cdot}CO{\cdot}NH_2$
$NH{\cdot}CO_2H{\cdot}NH_2{\cdot}CH_2{\cdot}CO{\cdot}NH_2$
(II.)

On the assumption that the carbamate (II) was first formed it was apparent that either (*a*) it had decomposed to aminoacetamide during the extraction, or (*b*) had itself been slowly extracted, yielding (I) on the subsequent addition of carbon disulphide.

$$R{\cdot}NH{\cdot}CO_2H{,}NH_2R + CS_2 \longrightarrow R{\cdot}NH{\cdot}CS_2H{,}NH_2R + CO_2 \qquad (R = CH_2{\cdot}CO{\cdot}NH_2)$$

It has now been found that the carbamate (II), formed in good yield by the action of carbon dioxide on an alcoholic solution of aminoacetamide, reacts readily with carbon disulphide in aqueous alcohol at room temperature to give the dithiocarbamate (I). The above reaction thus takes course (*b*). This is believed to be the first example of the conversion of a carbamate into the corresponding dithiocarbamate, although Inghilleri (*Gazzetta*, 1900, **30**, 634) described the reaction of carbon disulphide with ammonium carbonate under pressure at 100° to form ammonium thiocyanate, which might well have involved the initial conversion of the ammonium carbonate into ammonium carbamate followed by reaction with carbon disulphide and subsequent decomposition of the dithiocarbamate.

Benzylammonium benzylcarbamate (Wright and Moore, *J. Amer. Chem. Soc.*, 1948, **70**, 3865) similarly gives a good yield of the corresponding dithiocarbamate, but there has been no opportunity to extend the reaction to other carbamates.

The carbamate (II), m. p. 124·5° (decomp.) (uncorr.), is probably identical with the compound, m. p. 126° (decomp.), which is formed when aminoacetamide is exposed to air (Heintz, *Annalen*, 1868, **148**, 195; Koenigs and Mylo, *Ber.*, 1908, **41**, 4429; Cook, Heilbron, and Levy, *loc. cit.*) and was suspected of being a carbonate.

Experimental.

(All m. p.s are uncorrected.)

Carbamylmethylammonium Carbamylmethylcarbamate (II).—To a stirred suspension of aminoacetamide hydrochloride (30·0 g.) in absolute alcohol (180 ml.) at −5° 30% aqueous potassium hydroxide was added drop-wise till the reaction mixture was faintly alkaline (phenolphthalein). The mixture was filtered and the potassium chloride washed with a little absolute alcohol. Carbon dioxide was passed in a fairly rapid stream through the filtrate and washings, the temperature of the solution being conveniently kept at about 0° by the addition of small pieces of solid carbon dioxide. A practically colourless oil separated after a short time and separation appeared to be complete after about 2 hours. The oil crystallised when scratched, and the solid was filtered off, washed with alcohol and ether, and dried (14·38 g.); it had m. p. 124·5° (decomp.). The filtrate, on storage in the ice-chest overnight, yielded a further crop (9·42 g.), m. p. 123·5° (decomp.). *Carbamylmethylammonium carbamylmethylcarbamate* (10 g.) was recrystallised by dissolution in water (20 ml.) and addition of alcohol (75 ml.) followed by refrigeration, but the m. p. remained unchanged (Found: C, 31·2; H, 6·3. $C_5H_{11}O_4N_4$ requires C, 31·25; H, 6·25%). An aqueous solution gave no precipitate with barium chloride until warmed.

Reaction of Carbon Disulphide with Carbamylmethylammonium Carbamylmethylcarbamate.—To a solution of the carbamate (II) (5 g.) in water (10 ml.) and alcohol (20 ml.), carbon disulphide (2 ml.) was added. Slow evolution of carbon dioxide soon commenced and began to decrease after approx. 1·5 hours, when all the carbon disulphide had dissolved. Colourless crystals of carbamylmethylammonium carbamylmethyldithiocarbamate (I) rapidly separated at this point, and after a further hour at room temperature the mixture was cooled in the ice-chest and the solid (4·13 g., 71%) removed and washed with alcohol and ether. It had m. p. 139° (decomp.), not depressed on admixture with an authentic specimen; its identity was confirmed by conversion into 2-mercaptothiazolone by hydrochloric acid (Cook, Heilbron, and Levy, *loc. cit.*).

Reaction of Carbon Disulphide with Benzylammonium Benzylcarbamate.—Benzylammonium benzylcarbamate (5 g.) (Wright and Moore, *loc. cit.*) similarly gave the dithiocarbamate (4·42 g., 78·7%), m. p. 115° (decomp.) (heating from 110°), not depressed on admixture with an authentic specimen, m. p. 115° (decomp.) (heating from 110°), prepared from carbon disulphide and benzylamine in alcohol [Salkowski, *Ber.*, 1891, **24**, 2725, gave m. p. about 119° (decomp.)] (Found: C, 62·2; H, 6·2; N, 9·6; S, 22·8. Calc. for $C_{15}H_{16}N_2S_4$: C, 62·1; H, 6·2; N, 9·7; S, 22·1%).

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440. *Frog-spawn Mucin.*

By B. F. Folkes, R. A. Grant, and J. K. N. Jones.

Frog-spawn mucin, which contains some 42% of carbohydrate, on hydrolysis yields L-fucose (7·1%), D-mannose (3·5%), D-glucose (?), xylose (?), D-galactose (12·7%), D-glucosamine (8·9%), and D-chondrosamine (9·8%). Reaction of the mucin with periodate results in the destruction of the fucose and of some of the amino-sugars. Eighteen amino-acids have been identified after hydrolysis of the mucin, and the amounts determined quantitatively.

The analysis of the mucins (protein polysaccharide complexes) has been delayed by the lack of suitable methods for the quantitative determination of amino-acids and sugars. For example, the separation and identification of the sugars produced on hydrolysis is a matter of some difficulty owing to the interfering effect of the amino-acids and peptides produced simultaneously. The development of new methods (Hough, Jones, and Wadman, *J.*, 1949, 2511) has facilitated the separation of the sugars and we now report the results of an examination of the sugars and amino-acids produced on hydrolysis of frog-spawn mucin (cf. Giacosa, *Z. physiol. Chem.*, 1882, **7**, 40; Schulz and Ditthorn, *ibid.*, 1900, **29**, 373). This material is known to contain D-galactose (van Ekenstein and Blanksma, *Chem. Weekblad*, 1917, **4**, 407; Piric, *Brit. J. Exp. Path.*, 1936, **17**, 273; cf. Bray, Henry, and Stacey, *Biochem. J.*, 1946, **40**, 124) and fucose (Bray and James, 1st International Congress of Biochem., Abs. 267/6, 225) and it was of interest to determine whether L-galactose was also present as had been observed in snail galactogen (Baldwin and Bell, *J.*, 1938, 1461; 1941, 125). A preliminary examination of the products of hydrolysis of the mucin showed the presence of fucose, galactose, and glucosamine, provisionally identified on the paper chromatogram by the method of Partridge (*Biochem. J.*, 1948, **42**, 238). In order to confirm the identification of these sugars the mucin was hydrolysed, the acid and acidic amino-acids were removed with Amberlite resin IR4B, and the residual neutral and basic compounds separated on a column of cellulose, *n*-butanol half-saturated with water being used as eluent. In this manner the following sugars were isolated.

(*a*) L-Fucose was identified as the crystalline sugar and as its characteristic crystalline toluene-*p*-sulphonylhydrazone. The optical rotation of the crude sugar (−68°) showed that either some D-fucose or some other more positively rotating material was present. As the fraction gave a positive ninhydrin reaction this may have been amino-acid. *N*-Acetylglucosamine moves at the same rate as fucose on the chromatogram and may have been a contaminant.

(*b*) D-Mannose, was isolated as the characteristic phenylhydrazone. A solution of the phenylhydrazone in dilute hydrochloric acid furnished D-mannose, which behaved on the chromatogram in a manner identical with that of an authentic specimen of D-mannose phenylhydrazone treated in a similar fashion. This sugar and D-glucose were not detected in the preliminary hydrolysis experiments owing to their low concentration. Separation of the sugar mixture on a column, however, leads to concentration of the sugars, which can then be detected.

(*c*) D(?)-Glucose was identified as its osazone and by its rate of movement on the chromatogram. The low rotation of this fraction (+27°) indicated that other material, some of which was amino-acid, was also present.

(*d*) D-Galactose was isolated as the crystalline sugar. No L-galactose could be detected.

(*e*) D-Glucosamine hydrochloride. The identity of this material was confirmed by its conversion into D-glucosazone and by the identity of its *X* ray photograph with that of an authentic specimen.

(*f*) D-Chondrosamine was isolated as its crystalline hydrochloride which, with phenylhydrazine and acetic acid, gave galactosazone. The *X*-ray photograph was identical with that of an authentic specimen of chondrosamine hydrochloride. This amino-sugar was an unexpected component of the sugar mixture (cf., however, Schmidt, "Organic Chemistry," 5th edn., p. 812). Its separation from glucosamine on the chromatogram is unreliable and it escaped detection in the early experiments. Fucose, galactose, glucosamine, and chondrosamine have been detected in frog-spawn mucin by Drs. H. G. Bray and S. P. James (private communication). Xylose may also be present (see p. 2139).

The positions of the sugars on the chromatogram were revealed by spraying with *p*-anisidine hydrochloride solution in *n*-butanol (Hough, Jones, and Wadman, *J.*, 1950, 1702). The sites of the amino-sugars were shown by spraying duplicate papers with ninhydrin solution or Ehrlich's reagents. The yields of sugars obtained from the separation on the column of cellulose enabled an estimate of the percentages of the sugars present in the original mucin to be made. A more accurate determination of the sugars was made by analysis of the products of hydrolysis

of the mucin by the method of Flood, Hirst, and Jones (*J.*, 1948, 1679) as modified by Hirst and Jones (*J.*, 1949, 1659). The methyl pentose content of a sample of hydrolysed mucin was also determined by the method of Nicolet and Shinn (*J. Amer. Chem. Soc.*, 1941, **63**, 1456) and was found to be in close agreement with the fucose percentage determined as described above. The total amino-sugar content of a sample of hydrolysed mucin was checked colorimetrically by the method of Vasseur (*Arkiv Kemi*, 1949, **1**, 253): L-fucose, 7·1% (calc. as $C_6H_{12}O_4$), D-mannose, 3·5% (calc. as $C_6H_{12}O_6$), D-galactose, 12·7% (calc. as $C_6H_{12}O_6$), D-glucosamine, 8·9% (calc. as $C_6H_{11}O_4N$), and D-chondrosamine, 9·5% (calc. as $C_6H_{11}O_4N$).

The mucin was oxidised with sodium periodate solution with the resultant destruction of all the fucose and of some of the amino-sugar. During the oxidation formic acid was produced in amount corresponding to the formation of approximately one mol. of acid per mol. of fucose, indicating that this sugar is in the pyranose form and that it is an end group. The majority of the galactose appeared to be unaffected, and some of this fraction is therefore probably linked either through $C_{(3)}$ or through $C_{(2)}$ and $C_{(4)}$. The identity of the unoxidised amino-sugars remains to be determined. The amino-sugars are present very probably as *N*-acetyl derivatives (Found: *N*-acetyl, 9·4; this figure is high and other volatile acids may be present). The above evidence indicates that some 50% of the amino-sugar (if in the pyranose form) is present as end group, or is linked through $C_{(1)}$ and $C_{(4)}$ only. The glucose detected on the chromatogram may be part of the carbohydrate moiety of the mucin or it may result from the hydrolysis of a small amount of glycogen present as impurity. The method of isolation of the mucin, involving as it does a treatment of the frog spawn with 0·01N-sodium hydroxide at 35—40°, may result in the liberation of some of the glycogen which is present in the embryo. The mucin gave no detectable intensification of colour with aqueous iodine; the amount of glycogen admixed with the mucin must therefore be small. The carbohydrate moiety resembles the carbohydrate material obtained from other sources by Bray, Henry, and Stacey (*loc. cit.*) and by Aminoff, Morgan, and Watkins (*Biochem. J.*, 1950, **46**, 426). The latter authors have reported the presence of hexosamine, galactose, and fucose in the molecular proportions 2 : 1 : 1 in blood group A substance isolated from pseudomucinous ovarian cyst fluid. No mannose was detected.

The amino-acid content of the mucin was determined after hydrolysis with hydrochloric acid or sodium hydroxide. The majority of the amino-acids, provisionally identified by two-dimensional chromatography (Dent, *Biochem. J.*, 1948, **43**, 169), were determined by a modification (Folkes and Yemm, to be published) of the microbiological assay of Henderson and Snell (*J. Biol. Chem.*, 1948, **172**, 15). Alanine and threonine were determined by colorimetric estimation of the acetaldehyde produced on oxidation with ninhydrin (Virtanen and Rautanen, *Biochem. J.*, 1947, **41**, 101) and periodic acid (Winnick, *J. Biol. Chem.*, 1942, **142**, 461), respectively. Colorimetric tests (McFarlane and Guest, *Canadian J. Res.*, 1939, *B*, **17**, 139) for hydroxyproline yielded negative results. Amide nitrogen was determined by dilute acid hydrolysis followed by colorimetric estimation of the ammonia produced (Yemm and Folkes, to be published).

The results are given in the table (p. 2140). The amino-sugars, amino-acids, and amides account for nearly 94% of the total nitrogen. The threonine estimate may be slightly high, since traces of L-fucose which might have survived the severe hydrolysis conditions employed would also yield acetaldehyde on periodate oxidation. The cystine and methionine, as determined, contain only 90% of the total sulphur. The difference is probably due to the destruction of cystine during hydrolysis.

The ammonia content (12·4% of the total N) of the acid hydrolysate is much higher than would be expected from the amide content (6·3% of the total N), even after allowance for slight destruction of the hydroxyamino-acids. Experiments with glucosamine have shown that *ca.* 21% of its nitrogen is liberated as ammonia when it is subjected to the conditions employed to hydrolyse the mucin. If the same rate of destruction of the amino-sugars operates during the hydrolysis of the mucin, then some 4% of its total nitrogen would be liberated as ammonia.

The physical properties of the mucin and the comparatively small amount of material available rendered attempts to determine its homogeneity unsatisfactory. The results quoted above are, therefore, given with reserve, as more than one mucin or protein may be present. Moreover, some 10—15% of the mucin has not been identified. Some of this may be solvent as it has been found very difficult to remove the last traces of moisture even under reduced pressure at 100°. It is apparent, however, that the carbohydrate portion differs from the plant gums and mucilages in that it contains hexosamine residues. No uronic acid was detected. No evidence is available as to the mode of linkage of the carbohydrate and protein portions of the mucin, nor can much be said about the mode of linkage of the sugars, except that

fucose is an end group and that some of the galactose is linked through at least two carbon atoms.

In a private communication, Drs. H. G. Bray and S. P. James, of Birmingham University, inform us that they have also examined the hydrolysis products of a mucin obtained from frog spawn by dissection. The carbohydrate moiety appears to contain chondrosamine as the major amino-sugar component, along with galactose and fucose. Scission of the mucin with 0·05*M*-sodium carbonate at 100° for 5 minutes liberates a portion of the amino-sugar. Serine, glycine, threonine, alanine, lysine, proline, valine, leucine, aspartic acid, glutamic acid, arginine, cysteine (as cysteic acid) and phenylalanine were also detected in the acid hydrolysis products of the mucin by paper partition chromatography. Methylation of a mucin obtained by extraction of the spawn with barium hydroxide yielded an ether-soluble methylated product (A) which contained end groups of L-fucopyranose (7%) and D-galactopyranose (7%), identified as crystalline 2 : 3 : 4-trimethyl α-methyl-L-fucoside and 2 : 3 : 4 : 6-tetramethyl D-galactose anilide, respectively. Other partly methylated sugars await identification, but no amino-sugar derivatives were detected. The methylated derivative (A) probably represents a highly degraded fraction of the mucin.

It is apparent that much further work will be required to elucidate the structure of this mucin.

Experimental.

Isolation of the Mucin.—Fresh frog spawn was washed and separated as completely as possible from water and organic debris. *N*-Sodium hydroxide was then added with stirring until the total concentration was 0·01*N*. relative to the volume of the frog spawn. The mixture of spawn and alkali was then warmed to 35—40°; the outer jelly then rapidly dissolved, allowing the inner black embryo to settle out. The alkaline solution of mucin was decanted from the embryos and immediately made slightly acid by addition of acetic acid. The mucin was precipitated by pouring it into methanol (5 vols.), separated by decantation, washed by decantation with methanol and then with acetone, and collected on a filter. It was dried under reduced pressure at room temperature, and was obtained as a white powder insoluble in cold water, soluble in sodium hydroxide [Found: C, 40·6; H, 6·8; N, 8·1 (Dumas), 8·0 (Kjeldahl); S, 0·95; *N*-acetyl, 9·4; sulphated ash, 3·6%, on a sample dried at 100°/16 mm.].

Analysis of the Mucin.—The dried mucin (57 mg.) was dissolved in hydrochloric acid (2*N*.) and hydrolysed in a sealed tube at 100° for 7 hours. The tube was then cooled and opened, and the solution evaporated to a syrup under reduced pressure in order to remove most of the hydrochloric acid. The solution was then neutralised and the volume adjusted to 20 c.c. The amino-sugar content was determined colorimetrically on 4 c.c. of solution by the method of Vasseur (*loc. cit.*) (Found: 2·91 mg. of amino-sugar hydrochloride. This corresponds to the presence of 21% of amino-sugar, calculated as $C_8H_{15}O_6N$ and chondrosamine and glucosamine being assumed to give the same colour intensity per unit weight).

The mucin (34·2 mg.) was suspended in *N*-hydrochloric acid (10 c.c.), and the mixture heated on the boiling-water bath. At intervals, portions (1 c.c.) were withdrawn and the reducing power determined by the method of Hirst, Hough, and Jones (*J.*, 1949, 928) [Found: mg. of hexose liberated per c.c., 1·07 (35 minutes); 1·46 (2½ hours); 1·43 (3½ hours)]. This correspond to the liberation of 14·3 mg. of hexose or 37·6% of reducing sugar (as $C_6H_{10}O_5$). The solution was heated for a further 8 hours.

To the remaining solution (6 c.c.; equivalent to 20·5 mg. of mucin), rhamnose hydrate (4·17 mg.) was added and the cooled solution was neutralised with Amberlite resin IR4B and filtered. The filtrate and washings were evaporated to a syrup, and the sugars separated chromatographically on paper in the usual manner (Found, in duplicate experiments: rhamnose hydrate, 0·273, 0·300; fucose, 0·111, 0·111; mannose, 0·054, 0·054; galactose, 0·187, 0·210; glucosamine as the hydrochloride, 0·163, 0·170; chondrosamine as the hydrochloride, 0·174, 0·182 mg.). These figures correspond to the presence of fucose, 7·4, 6·7% (calc. as $C_6H_{10}O_4$), mannose, 3·6, 3·3%, galactose, 12·6, 12·8% (both calc. as $C_6H_{10}O_5$), glucosamine, 9·1, 8·6%, and chondrosamine, 9·7, 9·2% (both calc. as $C_8H_{15}O_6N$). No great accuracy is claimed for these last two pairs of figures owing to the difficulty in separating completely the two amino-sugars on the chromatogram.

Determination of Methyl Pentose (Nicolet and Shinn, *loc. cit.*).—The dried mucin (78·1 mg.) was hydrolysed with 0·5*M*-sulphuric acid (5 c.c.) for 7 hours. The solution was neutralised with solid sodium hydrogen carbonate, and the acetaldehyde determined after oxidation with periodate solution (Found: acetaldehyde equivalent to 7·17 c.c. of 0·01*N*-thiosulphate solution, *i.e.*, 6·8% of fucose calc. as $C_6H_{10}O_4$).

Hydrolysis of the Mucin and Isolation of the Sugars produced—Method A. The mucin (1·082 g.) was suspended in water (40 c.c.), and *N*-hydrochloric acid (40 c.c.) added. The mixture was then heated on the boiling-water bath (temp. of solution, 87°) for 26 hours. The cooled solution, which was pale yellow, was filtered free from humic material, and the filtrate passed down a column of IR4B resin. The neutral effluent and washings were concentrated to a brownish syrup, which was dissolved in methanol (5 c.c.), and the solution placed on top of a column of hydrocellulose (1½" × 12"). *n*-Butanol, half-saturated with water, was then allowed to percolate down the column, and the effluent was collected automatically in small fractions (*ca.* 6 c.c.). The detection and identification of the sugars in the eluate were carried out by the method of Hough, Jones, and Wadman (*loc. cit.*). Complete separation of all the sugar fractions was attained.

The solvent was removed from each fraction by distillation under reduced pressure at 50°, and the residue dissolved in water, filtered, and the filtrate concentrated under reduced pressure. Six fractions were obtained.

(1) This fraction was obtained as a syrup which slowly crystallised. Determination of the sugar content showed the presence of 59 mg. of reducing material calculated as fucose, $[\alpha]_D$ −68° (*c*, 0·59 in water) (yield, 4·9%, calc. as $C_6H_{12}O_5$). The syrup was triturated with methanol and a sample of crystalline L-fucose (3 mg.), m. p. and mixed m. p. 144°, was obtained, $[\alpha]_D$ −82° ± 6° (*c*, 0·4 in water). The methanolic filtrate was warmed with an alcoholic solution of toluene-*p*-sulphonylhydrazine, and L-fucose toluene-*p*-sulphonylhydrazone was precipitated (72 mg.). It was recrystallised from methanol and had m. p. and mixed m. p. 175°. The low optical rotation of the crude sugar may be due to the presence of D-fucose or xylose (?). Some material which gave a positive ninhydrin reaction was present.

(2) Estimation of the sugar content of Fraction 2 showed the presence of mannose (16·4 mg.), $[\alpha]_D$ +14° (*c*, 0·14 in water) (yield, calc. as $C_6H_{12}O_6$, 1·4%). This sugar did not crystallise. Phenylhydrazine acetate solution (1 c.c.) was added to the syrup, and the solution set aside. After two days the supernatant liquid was withdrawn from the crystals of mannose phenylhydrazone which adhered to the bottom of the flask. The crystals were washed successively with water, alcohol, and ether and dried (m. p. and mixed m. p. 185°, decomp.). A sample of the phenylhydrazone was dissolved in a drop of warm hydrochloric acid (2N.), and the solution placed on a chromatogram. A sample of mannose phenylhydrazone was treated in the same fashion. After separation in the usual manner it was found that the sugar liberated from the phenylhydrazone had moved through the same distance as had mannose, and that it gave the same colour reactions when the chromatogram was heated after it had been sprayed with aniline trichloroacetate or *p*-anisidine hydrochloride.

(3) This fraction (15 mg., from the determination of reducing power) did not crystallise; $[\alpha]_D$ +27° (*c*, 0·15 in water). When its solution was heated with phenylhydrazine acetate solution, glucosazone was formed, identified by its characteristic crystalline shape. The syrup gave a positive ninhydrin reaction and may have contained amino-acid as well as sugar.

(4) Determination of the sugar content of this solution showed the presence of 148 mg. of material (12·3%), $[\alpha]_D$ +79° (*c*, 1·2 in water). On concentration, crystalline D-galactose (128 mg.) was obtained, m. p. and mixed m. p. 165°.

(5) The solution obtained on concentration of this fraction was too dark for polarimetric observations. On standing, crystals of glucosamine hydrochloride separated. These were filtered off, washed with methanol, and dried (yield 108 mg., 7·5%, calc. as $C_6H_{13}O_5N$), $[\alpha]_D^{20}$ +72° (*c*, 1·0 in water). When a sample was heated with phenylhydrazine acetate solution, characteristic crystals of glucosazone were produced. An *X*-ray photograph of the crystals of the hydrochloride was identical with that obtained from a sample of authentic glucosamine hydrochloride.

(6) The solution obtained on concentration of this fraction was brown, and polarimetric observation was not possible. Concentration of the solution gave crystalline chondrosamine hydrochloride, which was separated by trituration with methanol, $[\alpha]_D^{20}$ +109° (*c*, 1·0 in water) (yield 93 mg., 6·4%, calc. as $C_6H_{11}O_4N$). A specimen of this material when heated with phenylhydrazine acetate solution gave galactosazone (characteristic crystals and solubility). An *X*-ray photograph of the crystalline amino-sugar hydrochloride differed markedly from that obtained from glucosamine hydrochloride (cf. Cutler, Haworth, and Peat, *J.*, 1937, 1979), and was identical with that obtained from authentic chondrosamine hydrochloride (Stacey, *J.*, 1944, 272).

Method B. The mucin (0·74 g.) was boiled with methanolic hydrogen chloride (50 c.c.; 2%) for 16 hours. The cooled solution was filtered, and the filtrate neutralised with silver carbonate and again filtered. The solution of glycosides and of esters of amino-acids was concentrated to a syrup, and the residue dissolved in water. When the solution was percolated down a column of IR100H Amberlite resin, practically all the amino-acid derivatives were removed. The eluate was concentrated to a syrup, which was dissolved in N-sulphuric acid (50 c.c.), and the dark solution heated on the boiling-water bath for 12 hours. The cooled solution was exactly neutralised with barium hydroxide and filtered. Concentration of the filtrate gave a syrupy residue (0·20 g.), which was separated on a column of cellulose, *n*-butanol half saturated with water being used as eluent. This led to the isolation and identification of samples of L-fucose and D-mannose. Xylose (5 mg.) was provisionally identified as its dibenzylidene dimethyl acetal, m. p. 205°, by its rate of movement on the chromatogram, and by the red colour produced by it on the chromatogram when warmed with aniline phthalate. The xylose may be an artefact and not a component of the mucin. No uronic acid was present (naphtharesorcinol test).

Oxidation of the Mucin by Periodate.—(a) The mucin (551 mg.) was suspended in water (50 c.c.), and 0·01N-sodium hydroxide (7 c.c.) added to make the solution neutral to "screened" methyl-red. The solution was cooled to 0°, and sodium periodate solution (7 c.c., 0·5M.) added. The solution was kept at 2° in the dark for 30 hours. (The oxidation of starch proceeds to completion under these conditions; Halsall, Hirst, and Jones, *J.*, 1947, 1390.) Ethylene glycol was added, and the solution titrated with 0·1N-sodium hydroxide (Found: 4·01 c.c., corresponding to the production of one mol. of formic acid per mol. weight 1380). This amount of formic acid would be produced from 11·8% of hexose end group (calc. as $C_6H_{10}O_4$) or from 10·6% of methyl pentose end group (calc. as $C_6H_{10}O_4$).

(b) The mucin (226·3 mg.) was oxidised with sodium periodate solution (10 c.c.; 0·5M.) as described above. Excess of periodate was removed by addition of ethylene glycol, and the solution dialysed until free from iodate ions. The solution was concentrated under reduced pressure, and a portion (115 mg.) of the pale yellow solid residue (140 mg.) hydrolysed in a sealed tube with N-hydrochloric acid at 100° for 7 hours. The volume was adjusted to 10 c.c. A portion (2 c.c.) of the cooled solution was neutralised with Amberlite resin IR4B, and the solution filtered and concentrated to a syrup. Examination of the syrup on the chromatogram showed the absence of fucose and the presence of a trace

of mannose and glucose. An intense spot corresponding to the presence of galactose was detected. On spraying with Ehrlich's reagents two spots corresponding to glucosamine and chondrosamine were detected, the former of lower intensity than the latter. Colorimetric determination on a portion of the solution showed the presence of *ca.* 11% of amino-sugar (calc. as $C_6H_{11}O_4N$).

Amino-acid Determinations.—The mucin (458 mg.) was heated in a sealed tube and in an autoclave at 15 lb. pressure with 3N-hydrochloric acid (10 ml.) for 5 hours. The solution was filtered to remove humin material and diluted to about 25 ml., the pH adjusted to 6·0 with sodium hydroxide, and the volume brought to 50 ml. with water. The solution was stored under toluene in a refrigerator until required. Total-nitrogen determinations (Kjeldahl) on 1-ml. aliquots showed 717, 718 μg. N/ml. [Calc. from total N of mucin (Kjeldahl 7·96, 7·98%): 731 μg. N/ml.]. The difference is assumed to be due to nitrogen bound in the humin material (lost during Kjeldahl determination). Free ammonia of 2-ml. aliquots was 90·1, 90·4 μg. N/ml. (12·35% of total N).

All the amino-acids estimations (with the exception of tryptophan and hydroxyproline) were carried out on this hydrolysate. Details of the methods employed are to be published elsewhere. Sixteen of the eighteen amino-acids were determined by a modification of the microbiological assay of Henderson and Snell (*loc. cit.*), *Leuconostoc mesenteroides* and *Lactobacillus arabinosus* being used as the assay organisms. All assays were carried out in triplicate at each of five levels of unknown and standard. Results are expressed in the table as mg. of amino-acid found per ml. of hydrolysate and as the calculated percentage of total nitrogen corresponding to each amino-acid.

Amino-acid calc. as:	Amino-acid, mg., per ml. of hydrolysate.	Total N, %.
Acid hydrolysate (total N, 731 μg./ml.).		
Alanine	0·142	3·1
Arginine (HCl)	0·166	6·1
Aspartic acid	0·359	5·2
Cystine	0·118	1·9
Glutamic acid	0·363	4·7
Glycine	0·474	12·1
Histidine (H_2O, HCl)	0·101	2·8
*iso*Leucine	0·225	3·3
Leucine	0·236	3·5
Lysine (HCl)	0·192	4·0
Methionine	0·209	2·7
Phenylalanine	0·125	1·5
Proline	0·325	5·4
Serine	0·210	3·8
Threonine	0·174	2·8
Tyrosine	0·137	1·5
Valine	0·154	2·5
Alkaline hydrolysate (total N, 185·8 μg./ml.).		
Tryptophan	0·0081	0·6
Amide N	—	6·3
Amino-sugars	—	20·0
	Total	93·8

Alanine was determined by oxidation with ninhydrin (Virtanen and Rautanen, *loc. cit.*) followed by estimation of the acetaldehyde produced by a modification of Stotz's *p*-hydroxydiphenyl colour reaction (*J. Biol. Chem.*, 1943, **148**, 585). Winnick's method (*loc. cit.*) was followed for the threonine estimations, *viz.*, oxidation with periodic acid in Conway micro-diffusion units and determination of acetaldehyde by the *p*-hydroxydiphenyl method.

Determination of Tryptophan. (With Miss J. C. Hillman).—The mucin (93·2 mg.) was hydrolysed by 17 hours' autoclaving in a sealed tube with 5N-sodium hydroxide (1 ml.). After adjustment with hydrochloric acid to pH 6·0, the volume was made up to 40 ml. (Calc. total N, 185·5 μg./ml.). Tryptophan was determined by microbiological assay, *L. arabinosus* being used. Complete racemisation was assumed to have taken place during hydrolysis, and DL-tryptophan was employed as the standard.

Test for Hydroxyproline.—A hydrolysate was prepared by heating 200 mg. of the mucin with 3N-sulphuric acid (2 ml.) in a sealed tube at 100° for 12 hours. After neutralisation, the solution was filtered and made up to 5 ml. 1-Ml. aliquots were employed for the colour test (McFarlane and Guest, *loc. cit.*) but no hydroxyproline could be detected; neither was it detected on the chromatogram.

Determination of Amide Nitrogen.—Weighed portions of the mucin (16·05, 13·50 mg.) were hydrolysed with 2N-sulphuric acid (10 ml.) at 100° for 3 hours. The ammonia produced was distilled off and determined by Nesslerisation (Found: N, 796, 683 μg., corresponding to an amide content of 6·23, 6·35% of total N).

Destruction of Glucosamine on Acid Hydrolysis.—D-Glucosamine hydrochloride (70 mg.) was autoclaved in a sealed tube at 15 lb. pressure for 5 hours with 3N-hydrochloric acid (2 ml.). The solution was diluted to 10 ml., and 1 ml. aliquots were taken for the determination of free ammonia (Found: 92, 96 μg. ammonia N/ml., equivalent to 20, 21% of the total nitrogen of the glucosamine).

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441. *The Sommelet Reaction. Part III. The Choice of Solvent and the Effect of Substituents.*

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Electron-attracting substituents decrease the rate and the yield of the Sommelet reaction even when electron-releasing substituents are also present. Best conditions are given for the preparation of thirteen aldehydes, including phenolic aldehydes and dialdehydes. 50% Acetic acid solution is introduced as the best solvent for the Sommelet reaction.

Aromatic aldehydes, substituted by halogens or alkyl or alkoxy-groups, are readily prepared by the Sommelet reaction (cf. Part I, *J.*, 1949, 2700; Part II, *ibid.*, p. 2704). The effect of a nitro-group has been studied by Mayer and English (*Annalen*, 1918, **417**, 63) who failed to prepare *o*- and *p*-nitrobenzaldehyde from the corresponding benzyl chlorides. Graymore (*J.*, 1947, 1118), however, obtained *p*-nitrobenzaldehyde in poor yield from *p*-nitrobenzylmethyleneamine. As no other aldehyde with a strongly electron-attracting group (NO_2, CHO, COMe, SO_2NH_2) appears to have been prepared by the Sommelet method we have decided to study the effect of such substituents.

It soon became apparent that electron-attracting substituents have an unfavourable effect on the Sommelet reaction. It has been shown in Part I (*loc. cit.*) that the reaction of an arylmethyl halide with hexamine proceeds in three steps: (i) a quaternary compound, the hexaminium halide, is formed, (ii) this is hydrolysed to an arylmethylamine, and (iii) the amine is converted into an aldehyde (the Sommelet reaction proper). Our preparative experience indicated that the rate of (i) was decreased by electron-attracting substituents, and this conclusion was confirmed by semi-quantitative rate measurements. A *p*-chloro-substituent has a slight, a *p*-nitro-substituent a pronounced effect. Step (ii) is fast in comparison with the others. The velocity of step (iii) shows very little substituent effect but it is characteristic for negatively substituted aldehydes that yields show a maximum at a definite reaction time and drop off sharply on prolonged heating (cf. Nos. 7 and 8 below, and Table II). The m. p. of the crude product is also decreased, indicating that the aldehyde participates in side reactions. The time of heating is therefore critical in the preparation of aldehydes with electron-attracting groups; with other aldehydes no such difficulty was encountered.

It follows from these facts that, when the hexaminium salt is formed during the Sommelet reaction, the slowness of this step necessitates prolonged heating which reduces the yield and purity of the aldehyde. It is therefore imperative in many cases to prepare and isolate the hexaminium salt first by heating the reactants in chloroform solution which may be done for any length of time without fear of side-reactions.

It was also found that the usual solvent, aqueous ethanol, gave poor yields in many cases. A better reaction medium was therefore sought.

The Choice of Solvent.—Hewett (*J.*, 1940, 297) introduced glacial acetic acid as a solvent for the Sommelet reaction and Badger (*J.*, 1941, 535) prepared the two naphthaldehydes in good yield by this method from the bromomethylnaphthalenes. Very concentrated solutions were employed with a boiling time of only 0·5—1 minute. When we repeated this procedure with 1-chloromethylnaphthalene much of it was recovered unchanged. Ten minutes' heating resulted in the disappearance of the starting material but the yield of aldehyde was poor and decreased further on longer boiling. At the concentration used, the boiling point of the mixture was over 160° and it was apparent that decomposition of the aldehyde occurred. This was confirmed in the case of benzaldehyde: after 1 hour's boiling with hexamine in glacial acetic acid less than one third was recovered. Besides tarry products, benzylamine and benzylmethylamine were formed, *i.e.*, a reversal of the Sommelet reaction had taken place. No such effect was noticed with lower-boiling solvents. Acetic acid should therefore be used with care; the solution should contain at least 5 parts of solvent for each part of hexamine, and boiling be as short as possible.

To carry out the reaction at a lower temperature, 50% acetic acid solution was used as reaction medium. This solvent seems to combine a suitable boiling point with good solvent power and a desirable acidity. The Sommelet reaction [step (iii)] is faster in this medium than, at the same temperature, in aqueous ethanol. In most cases, though not in all, it proved to be the best solvent. It has the disadvantage, however, that it rapidly hydrolyses hexamine, *e.g.* a 70% yield of 1-naphthaldehyde fell to 23% when the solution of hexamine in 50% acetic acid was boiled for 15 minutes before the addition of 1-chloromethylnaphthalene. This can be overcome by the use of excess of hexamine in those cases where the hexaminium salt is formed

TABLE I.

Preparation of aldehydes.

Aldehyde.	Halogenomethyl compound,	Hexaminium salt [a] (g.).	Hexamine (g.).	Solvent,	c.c.	Time of heating (hrs.).	M. p., crude.	M. p., pure.	Crude yield [b, c] (%).
1. 1-Naphthaldehyde	1-$C_{10}H_7$-CH_2Cl	50	—	79	50% AcOH	235	2	1—2·5°	2·5° [d]	82 [e]
		10	—	8·5	AcOH	30	½	—		30 [e]
		10	—	10 [f]	60% EtOH	60	2	—		72 [e]
2. *p*-Nitrobenzaldehyde	*p*-NO_2-C_6H_4-CH_2Cl	—	20	—	50% AcOH	100	1	105	106	59
3. *o*-Nitrobenzaldehyde	*o*-NO_2-C_6H_4-CH_2Cl	—	10	—	50% AcOH	50	2	36—38	44	36 (17)
4. *m*-Nitrobenzaldehyde	*m*-NO_2-C_6H_4-CH_2Cl	—	10	—	50% AcOH	50	2	51—52	58	45 (35)
5. 2 : 4-Dinitrobenzaldehyde	2 : 4-$(NO_2)_2$-C_6H_3-CH_2Cl	—	10	—	50% AcOH	50—80	1—2	—	—	0
6. *p*-Sulphamylbenzaldehyde [g]	*p*-NH_2SO_2-C_6H_4-CH_2Cl [h]	—	10	1·6	50% AcOH	33	5	102—104	118	21 (0)
		10	—	7·8 [i]	50% AcOH	50	5	113—114		19 (0)
7. 3-Nitro-4-hydroxybenzaldehyde	3 : 4 : 1-NO_2-C_6H_3(OH)-CH_2Cl [j]	10	—	10	AcOH	100	½	139—141	144·5	70 (66)
		10	—	10	50% AcOH	100	1½	139—141		41
8*a*. 5-Nitrosalicylaldehyde	3 : 6 : 1-NO_2-C_6H_3(OH)-CH_2Cl [j]	10	—	10 [k]	AcOH	100	1	122—123	126	57 (45)
		10	—	10	50% AcOH	125	2	122—123		37
8*b*.	3 : 6 : 1-NO_2-C_6H_3(OAc)-CH_2Cl [l]	—	10	—	50% AcOH	135	1½	122—124		34 (24)
9. 3-Chloro-4-hydroxybenzaldehyde	4 : 3 : 1-OH-C_6H_3Cl-CH_2Cl [m]	—	10	—	AcOH	25	½	115—120	139 (lit.)	22 (10)
10. 3 : 5-Dichlorosalicylaldehyde	2 : 3 : 5 : 1-OH-$C_6H_2Cl_2$-CH_2Cl [n]	—	20	—	AcOH	50	1	92—94	95	66
		10	—	10	AcOH	45	1	88—92		55 (51)
11*a*. 4-Hydroxyisophthalaldehyde	2 : 1 : 5-OH-C_6H_3(CHO)-CH_2Cl [o]	10	—	10	50% AcOH	55	1	108—109	113	63 (55)
11*b*.	4 : 1 : 3-OH-C_6H_3(CHO)-CH_2Cl [o]	10	—	10	60% EtOH	150	2½	105—108		30 (0)
		10	—	10	50% AcOH	100	1	106—107		25 (0)
12. 2-Methoxy-5-acetylbenzaldehyde [p]	2 : 5 : 1-MeO-C_6H_3(COMe)-CH_2Cl [q]	10	—	10	60% EtOH	35	4	137—140 [r]	144	28 (0)
13. Terephthalaldehyde	*p*-$C_6H_4(CH_2Cl)_2$	—	10 [s]	3·6	50% AcOH	85	2	114	116	34
14. Phthalaldehyde	*o*-$C_6H_4(CH_2Br)_2$	—	10	—	50% AcOH	30—50	½—2	—	—	0
15. 2 : 5 : 1 : 4-*Dimethoxyterephthalaldehyde*	2 : 5 : 1 : 4-$(MeO)_2C_6H_2(CH_2Cl)_2$ [t]	—	10	—	50% AcOH	50	1	206	207	32 (29)
		—	10	—	AcOH	50	½	204—206		28 (25)

a. Preparation given in Experimental Section. *b*. The yields are based in all cases on chloromethyl compounds, not on hexaminium salts. *c*. The figure in parentheses indicates the amount which crystallised out of the reaction mixture. The rest was obtained by extraction with ether (3, 4, 6, 9, 12), ethyl acetate (7, 8, 10), or chloroform (11, 15). *d*. The m. p. (33—34°) given by Stephen (*J.*, 1925, **127**, 1877) is erroneous. Repeated purification through the bisulphite compound and by distillation failed to raise the m. p. above 2·5°. The semicarbazone had the m. p. given by Stephen (222°). *e*. The aldehyde was extracted with ether and distilled; b. p. 160—163°/18 mm. *f*. More hexamine (5 g.) was added after 1·5 hours' boiling. *g*. Burton and Hu, *J.*, 1948, 603. *h*. Angyal and Jenkin, *Aust. J. Sci. Res., A*, 1950, in press. *i*. Formaldehyde (3·4 c.c.; 40%) was added. *j*. Buehler, Kirchner, and Diebel, *Org. Synth.*, 1940, **20**, 59. *k*. The intermediate 3-nitro-6-hydroxybenzylmethyleneamine has a low solubility and separates after a short time. To avoid bumping, the yellow precipitate was dissolved by the addition of concentrated hydrochloric acid (15 c.c.) as soon as it appeared. *l*. Jacobs and Heidelberger, *J. biol. Chem.*, 1915, **20**, 659. *m*. Buehler, Brown, Holbert, Fulmer, and Parker, *J. Org. Chem.*, 1941, **6**, 902. *n*. Recrystallised from ethanol. *o*. Gray and Bonner, *loc. cit.* *p*. The hexaminium salt was added to the boiling solution in small portions during 0·5 hour. *q*. Wood and Gibson, *J. Amer. Chem. Soc.*, 1949, **71**, 393.

TABLE II. p-*Nitrobenzaldehyde from* 20 *g. of* p-*nitrobenzylhexaminium chloride.*

Solvent,	c.c.	Time (mins.).	Yield (g.).	M. p. (crude).	Solvent,	c.c.	Time (mins.).	Yield (g.).	M. p. (crude).	Solvent,	c.c.	Time (mins.).	Yield (g.).	M. p. (crude).
AcOH	20	2	2·6	98—99°	AcOH	50	20	4·0	97—98	50% AcOH	200	30	3·5	105
AcOH	20	30	2·7	95—98	AcOH	100	10	4·0	105	50% EtOH	60	60	2·2	105
AcOH	50	10	5·9	103	50% AcOH	100	60	6·3	105	Water	250	60	2·4	105

rapidly. When this formation is slow, the hexaminium salt can be prepared in chloroform and then heated in 50% acetic acid solution; hydrolysis is then no disadvantage because it is not hexamine itself but its hydrolysis products which react in step (iii).

Thus, the procedure which is most likely to give good results in yet untried cases is to prepare the hexaminium salt in chloroform and then heat it with 50% acetic acid solution.

The Effect of Substituents.—Details of the preparation, and yields, of fifteen aldehydes are summarised in Table I. Where the hexaminium salt was isolated, this is indicated in the table by showing the amount of this salt used in the reaction. The conditions given in the table represent for each aldehyde (except Nos. 3 and 4 for which the optimum conditions were not ascertained) the highest yield obtained from at least ten runs in which the solvent, the concentration, and the time of heating were varied. In some cases the conditions giving the best yield in another solvent are also given for comparison.

The effect of varying conditions on the yield is shown in Table II for *p*-nitrobenzaldehyde. Runs made without isolating the hexaminium salt gave low yields and impure product. The by-products were, as usual, *p*-nitrobenzylamine and *p*-nitrobenzylmethylamine.

1-Naphthaldehyde has been prepared several times previously by the Sommelet reaction (Mayer and Sieglitz, *Ber.*, 1922, **55**, 1846; Anderson and Short, *J.*, 1933, 485; Coles and Dodds, *J. Amer. Chem. Soc.*, 1938, **60**, 853; Rupe and Brentano, *Helv. Chim. Acta*, 1936, **19**, 586; Ruggli and Preuss, *ibid.*, 1941, **24**, 1350; Badger, *loc. cit.*; Price and Voong, *J. Org. Chem.*, 1949, **14**, 115). It is included here because of the thorough study we made of the reaction conditions, resulting in greatly improved yield. It was found that methylation to 1-(methylaminomethyl)naphthalene was slow (cf. Part I) and the yield was therefore not materially improved by dropwise addition of chloromethylnaphthalene. The Sommelet reaction is the best method of preparation of this aldehyde.

For the preparation of No. 6, the corresponding amine ("Marfanil") was used in most runs because of its availability. It has been ascertained in several cases that the use of an amine hydrochloride, with 1 mol. of hexamine and 1 mol. of formaldehyde, is equivalent to the use of the corresponding hexaminium salt. The low yield in this case is probably due to side-reactions between the sulphonamide group and formaldehyde since amorphous by-products were formed.

Whilst one electron-attracting group reduces the yield of the Sommelet reaction, two apparently inhibit it completely (No. 5). Introduction of an additional hydroxy-group, which accelerates the hexaminium salt formation enormously, has little effect on step (iii). Indeed, in its effect a hydroxy-group is not different from an acetoxy-group, as is shown by comparison of Nos. 8*a* and 8*b*. In the latter the acetyl group has been lost presumably during the acid hydrolysis following the reaction.

The relative position of the substituents is important, however, as is shown by a comparison of Nos. 7 and 8. When the hydroxy-group is in an *o*-position to the prospective aldehyde group, not only the yield but also the reaction rate is reduced. Thus in glacial acetic acid, in the concentration given in the table, the best yield (70%) of No. 7 was obtained after 0·25 hour; on boiling for one hour the yield fell to 51%. In the same concentration, the yield of No. 8 after 0·25, 1, and 2 hours was 45, 57, and 36%, respectively. This effect is even more noticeable in the case of Nos. 11*a* and 11*b* where the same aldehyde was obtained in a lower yield from the isomer having a group *ortho* to the chloromethyl group.

The same effect is responsible for the low yield of 2-methoxy-5-acetylbenzaldehyde (No. 12). This aldehyde, the toxic principle of the leaves of *Encelia farinosa*, was synthetised by Gray and Bonner (*J. Amer. Chem. Soc.*, 1948, **70**, 1249) from *p*-methoxyacetophenone in four steps, using Stephen's aldehyde synthesis. Though the Sommelet reaction is unsatisfactory in this case, it still gives a much better overall yield from *p*-methoxyacetophenone than Gray and Bonner's method.

The Sommelet reaction is not applicable to phenolic compounds unless the activity of the ring is reduced by electron-attracting substituents (Nos. 7, 8, 11), otherwise condensation with formaldehyde occurs. One chlorine does not reduce the activity sufficiently, since No. 9 was obtained in poor yield and with such a low m. p. that purification was not practicable; it was identified only as the semicarbazone. When the benzene ring was substituted with two chlorine atoms (No. 10) yields were again satisfactory.

Dialdehydes.—The preparation of dialdehydes by the Sommelet reaction has not been described previously. A double Sommelet reaction on a bishalogenomethyl compound is feasible but because one aldehyde group acts as an electron-attracting substituent in the formation of the other, and because the incidence of side-reactions is also doubled, the yields are not particularly good. That formation of the second aldehyde group is slower is indicated in the preparation of

terephthalaldehyde by the isolation of a by-product which appears to be a polymeric Schiff's base of *p*-aminomethylbenzaldehyde.

While this work was in progress, a paper was read by Wood, Tung, Perry, and Gibson to the September, 1949 (Atlantic City), meeting of the American Chemical Society. In this paper, which is available to us in abstract only, they report the preparation of eleven bishexaminium salts of which six yielded dialdehydes. While waiting for the publication of their results we have suspended the work on dialdehydes. Their general conclusions agree with ours: *o*-dialdehydes were not obtained (cf. No. 14), and others only if at least one position adjacent to each aldehyde group was unsubstituted (cf. Part II, *loc. cit.*).

No. 15, 2 : 5-dimethoxyterephthalaldehyde, is remarkable for its intense yellow colour and strong fluorescence. The reason for its colour is similar to that for 2 : 5-dihydroxyterephthalic acid and its esters which were extensively studied by Hantzsch (*Ber.*, 1915, **48**, 797; 1917, **50**, 1213). The colour would nowadays be explained by resonance.

We were unable to prepare diphenyl-2 : 2'-dialdehyde by the Sommelet reaction. The reason for this failure is not clear but it may be the same as in the case of *o*-dialdehydes, *i.e.*, interaction of the adjacent functions. We hope to investigate this problem later.

Recently Hass and Bender (*J. Amer. Chem. Soc.*, 1949, **71**, 1767) described another method for the preparation of aldehydes from halogenomethyl compounds: the reaction with the sodium salt of 2-nitropropane. To compare the value of this method with the Sommelet reaction in the case of polysubstituted aldehydes it was tried for the preparation of Nos. 10, 11, and 12, but without success.

Experimental.

(M. p.s are corrected.)

Preparation of Aldehydes.—The hexaminium salts, or the halogenomethyl compounds and hexamine, in the amounts given in Table I, were boiled under reflux for the time indicated. Concentrated hydrochloric acid (350 c.c. for each mole of hexamine or hexaminium salt) was then added and boiling continued for another 5 minutes. If this acid treatment was omitted the aldehydes were sometimes contaminated by Schiff's bases. The reaction mixture was diluted with water and allowed to cool; the aldehydes crystallised out. Where a significant amount remained in solution it was recovered by solvent extraction as indicated in the table. It was not found necessary to purify any of the aldehydes by conversion into their bisulphite compounds.

Preparation of Hexaminium Salts.—The chloromethyl compound (0·1 mole) and hexamine (15·5 g.) were boiled under reflux in chloroform (100 c.c.), and the quaternary salt filtered off after the solution had cooled. Times of boiling and yields are given for the salts prepared from the following chloromethyl compounds: 1-chloromethylnaphthalene, 1 hour, 96%; 2 : 4-dinitrobenzyl chloride,* 5 hours, 74%; 3-nitro-4-hydroxybenzyl chloride, 1 hour, 96%, yellow, m. p. 174°; 3-nitro-6-hydroxybenzyl chloride,* 1 hour, 95%, yellow, m. p. 193° (decomp.); 3-nitro-6-acetoxybenzyl chloride, 7 hours, 70%, yellow, m. p. 191—193° (decomp.); 3-chloro-4-hydroxybenzyl chloride, 2 hours, 105%, m. p. 140—141° (this compound contained chloroform which could not be removed without decomposition); 3 : 5-dichloro-2-hydroxybenzyl chloride, 3 hours, 93%, m. p. 174—178° (decomp.); 5-chloromethylsalicylaldehyde,* 3½ hours, 90%, yellow, m. p. 178—182° (decomp.); 4-hydroxy-3-chloromethylbenzaldehyde, 3 hours, 94%, m. p. 184—185° (decomp.); 2-methoxy-5-acetylbenzyl chloride, 2 hours, 93%, m. p. 182° (decomp.). The salt marked by * were described by Jacobs and Heidelberger (*loc. cit.*) but without giving yields.

p-Sulphamylbenzylhexaminium chloride was prepared in alcohol according to Angyal and Jenkin (*loc. cit.*).

Since the nitrobenzylhexaminium chlorides are somewhat soluble in chloroform the yields were improved by removing, after 4 hours' boiling, half of the chloroform by distillation and adding an equal volume of acetone. Yields obtained thus from the nitrobenzyl chlorides were: *o*-, 89%*; *m*-, 89%*; *p*-, 91%.* Mayer and English (*loc. cit.*) reported 61% and 68% for the *o*- and *p*-derivative, respectively.

Since the bishexaminium salts decompose on being heated, they were prepared by adding the bishalogenomethyl compounds (0·1 mole) to a solution of hexamine (30 g.) in chloroform (330 c.c.) and leaving its solution at room temperature for two days. The salts were thus obtained from *p*-xylylene dichloride, 90%, m. p. 160—170° (decomp.); from *o*-xylylene dibromide, 71%; and from 2 : 5-dimethoxy-*p*-xylylene dichloride, 99%, m. p. 193—197° (decomp.).

The chloroform solutions of the two nitrohydroxybenzyl chlorides gave precipitates immediately on being mixed with a cold solution of hexamine in chloroform. These yellow precipitates were at first believed to be phenolic salts until it was found that they contained the chlorine in ionic form and were identical with the salts formed on boiling the reactants for an hour. All the other chloromethyl compounds having a hydroxy-group gave immediate precipitates with hexamine, some of which changed in appearance on being boiled; but it was not ascertained whether they were phenolic or quaternary salts. The activating effect of the hydroxy-group is eliminated by acetylation since 3-nitro-6-acetoxybenzyl chloride reacts only slowly with hexamine.

Comparative Reaction Rates.—(a) *Step* (i). Solutions of hexamine (1·4 g.) in chloroform (13 c.c.), warmed to 55°, were added to 0·01 mole each of benzyl, *p*-chlorobenzyl, and *p*-nitrobenzyl chlorides. After 30 minutes at 55°, ice-cold nitric acid (50 c.c.; 6%) was added with shaking, and the aqueous layer was separated and aliquots titrated for ionic chloride. Yields of salt were: benzyl, 31·5; *p*-chlorobenzyl, 30; *p*-nitrobenzyl, 10%.

(b) *Step* (iii). Solutions of hexamine (1·4 g.), amine hydrochloride (0·01 mole; benzyl- 1·44, *p*-chlorobenzyl-1·78, *p*-nitrobenzyl- 1·89 g.), and formaldehyde (0·1 c.c.; 40%) in 50% acetic acid (10 c.c.) were kept at 75° for 1 hour, then a mixture of hydrochloric acid (10 c.c.) and water (20 c.c.) was added. Benzaldehyde was removed by steam-distillation, oxidised by alkaline hydrogen peroxide, and weighed as benzoic acid. *p*-Chlorobenzaldehyde was extracted by ether, and *p*-nitrobenzaldehyde by benzene, and the extracts were washed with sodium carbonate solution and evaporated to dryness. Yields were: benzaldehyde, 18; *p*-chlorobenzaldehyde, 21; and *p*-nitrobenzaldehyde, 19%.

When benzylamine hydrochloride reacted under the same conditions in 80% ethanol, the yield was only 6%. Ethanol of lower concentration did not suffice to give a homogeneous solution. Comparison with the other two amines could not be made because, even from 80% ethanol, the Schiff's bases separated.

Reaction of Benzaldehyde with Hexamine in Acetic Acid.—Benzaldehyde (20 g.), hexamine (23 g.), and glacial acetic acid (70 c.c.) were refluxed for 1 hour, the temperature of the mixture being 140°. Addition of dilute hydrochloric acid and steam-distillation gave 6·3 g. of benzaldehyde. Steam-distillation was continued until all formaldehyde was removed. A heavy oil (6 g.) settled out from which no pure compound could be isolated. The supernatant liquid was concentrated, made alkaline with sodium hydroxide, and extracted with ether; evaporation of the solvent left 7·2 g. of amines. Distillation of these gave a fraction (2·0 g.), b. p. 76—82°/20 mm., a small amount of higher boiling material, and much undistillable residue. The distilled amines were treated with toluene-*p*-sulphonyl chloride and gave toluene-*p*-sulphonbenzylamide, m. p. 114°, and toluene-*p*-sulphonbenzylmethylamide, m. p. 94°, both identified by mixed m. p.s.

The By-products of the Sommelet Reactions.—The mother-liquor from the preparation of *p*-nitrobenzaldehyde (No. 2, Table I) was freed from formaldehyde by steam-distillation. Sodium hydroxide solution (150 c.c.; 5%) was added and the bases extracted with ether. Evaporation of the solvent yielded an oil (2·3 g.) which was treated with toluene-*p*-sulphonyl chloride (3 g.) in pyridine (27 c.c.). The sulphonamides were separated by treatment with hot sodium hydroxide solution (220 c.c.; 8%) and gave, after crystallisation from aqueous alcohol, toluene-*p*-sulphon-*N*-*p*-nitrobenzylamide (0·8 g.; m. p. 120°) and toluene-*p*-sulphon-*N*-*p*-nitrobenzyl-*N*-methylamide (3·2 g.; m. p. 127·5°) (Angyal, Morris, Rassack, Waterer, and Wilson, *J.*, 1949, 2722).

The By-product of the Preparation of Terephthalaldehyde.—The mother-liquor of No. 13 was freed from formaldehyde by steam-distillation and made alkaline with sodium hydroxide. A cream solid was precipitated which was insoluble in all solvents, soluble in acids, and on being heated charred without melting. With phenylhydrazine it gave a yellow precipitate.

3-*Nitro*-4-*hydroxybenzyl Chloride.*—Hydrogen chloride was passed into a well-stirred mixture of *o*-nitrophenol (100 g.), formaldehyde (167 c.c.; 40%), concentrated hydrochloric acid (760 c.c.), and concentrated sulphuric acid (10 c.c.) at 90—100° for 6 hours. After cooling, the mixture was extracted with benzene (250 c.c.), and the extract dried (Na_2SO_4) and evaporated under reduced pressure until crystallisation started. Addition of anhydrous ethanol (150 c.c.) and cooling gave the crude product, m. p. 68—69° (75 g., 56%). After crystallisation from benzene (50 c.c.) with the addition of light petroleum (250 c.c.) yellow needles were obtained (48 g.), m. p. 72—74°. D.R.P. 132,475 (Friedländer, **6**, p. 142) reported m. p. 75°.

5-*Chloromethylsalicylaldehyde.*—Hydrogen chloride was passed into a well-stirred mixture of salicylaldehyde (30 g.), formaldehyde (18·5 c.c.; 40%), and concentrated hydrochloric acid (255 c.c.), kept at 15—20° by external cooling, for 3 hours. The precipitated white solid was filtered off and dissolved in ether (250 c.c.), and the solution dried (Na_2SO_4). Evaporation *in vacuo* of most of the solvent gave two successive solid fractions (14 g. each); these were combined and quickly dissolved in hot light petroleum (500 c.c.; b. p. 40—70°) which left some oil. On cooling, the product (15 g.) was obtained in colourless needles, m. p. 85—86°. D.R.P. 114,194 (Friedländer, **6**, p. 139) reported m. p. 88°. By concentration of the mother-liquor another 5 g. were obtained which yielded 3 g. on recrystallisation (total yield 43%). Heating should be avoided at all stages of this preparation since it causes reddening of the product.

4-*Hydroxy*-3-*chloromethylbenzaldehyde.*—Hydrogen chloride was passed into a well-stirred mixture of *p*-hydroxybenzaldehyde (25 g.), formaldehyde (16 c.c.; 40%), and concentrated hydrochloric acid (180 c.c.) for 3 hours. The temperature rose to 40°, and a blood red solution was obtained which started to deposit a solid after 2 hours. Cooling, filtration, and crystallisation from chloroform (400 c.c.) gave the crude product, m. p. 129—131° (18·9 g.; 48%). It was crystallised from acetone (25 c.c.)–chloroform (50 c.c.) giving a solid (12·3 g.), m. p. 135—136°. For analysis, the *aldehyde* was crystallised from chloroform; it formed colourless needles, m. p. 138° (Found: Cl, 20·9. $C_8H_7O_2Cl$ requires Cl, 20·8%).

2-*Methoxy*-5-*acetylbenzyl Chloride.*—Hydrogen chloride was passed into a well-stirred mixture of *p*-methoxyacetophenone (37 g.), formaldehyde (23 g.; 40%), and concentrated hydrochloric acid (150 c.c.) at 45° for 4 hours. The colour of the mixture changed to dark red and after 3 hours a red solid began to separate. Cooling and filtration gave the crude product (40 g.), m. p. 112—114°, which was crystallised from benzene (160 c.c.)–light petroleum (60 c.c.) yielding a solid (28 g., 69%), m. p. 115—117°. For analysis, the *chloride* was recrystallised from benzene and then melted at 118° (Found: C, 61·35; H, 5·9. $C_{10}H_{11}O_2Cl$ requires C, 60·5; H, 5·6%).

2 : 5-*Dimethoxyterephthalaldehyde.*—This *compound* sublimes *in vacuo* to give a powder, m. p. 207°, of intense yellow colour (Found: C, 61·35; H, 5·3. $C_{10}H_{10}O_4$ requires C, 61·8; H, 5·2%). Its solutions in water or alcohol are yellow with a vivid fluorescence which disappears on the addition of strong acids or alkalis. The *dioxime*, m. p. 246—246·5°, is pale yellow (Found: N, 12·2. $C_{10}H_{12}O_4N_2$ requires 12·5%).

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442. *The Franck–Condon Principle and the Size of the Excited Benzene Molecule.*

By D. P. Craig.

The Franck–Condon principle applied to the experimental intensity distribution in the 2600 A. band system of benzene gives the value 0·037 A. for the increase in equilibrium C–C distance in the excited electronic state. This agrees well with values deduced by Garforth, Ingold, and Poole (*J.*, 1948, 508) from empirical relations between force constant and bond length.

The calculation of changes in molecular dimensions by means of the Franck–Condon principle may be carried out in various simplified ways. Two of these are examined. The assumption that CH groups are concentrated in mass points gives the value 0·036 A. If, in addition, it is assumed that the force constants are unchanged in the excited state, a value 0·035—0·036 A. is obtained. The last calculation demands no detailed information about the excited electronic state, and so may be applied to study changes in dimensions of more complicated molecules whose excited-state elastic constants are not known.

The intensity of an electronic transition is distributed in the bands of its band system in a definite way. Apart from a small dependence on the change in elastic constants, the intensity distribution is governed predominantly by the change in molecular dimensions in the two electronic states, and thus by the Franck–Condon principle. Given the change in the dimensions, and the elastic constants for the two combining states, the Franck–Condon principle allows the intensity distribution to be calculated. In diatomic molecules this was first done by Hutchisson (*Physical Rev.*, 1930, **36**, 410), who compared values for molecular hydrogen with experiment and got fair agreement in view of the difficulties of the experimental measurement. In Hutchisson's case of hydrogen, and rather generally with diatomic molecules, the dimensions of the combining states can be derived with great precision from the rotational structure of the bands, so that there is no need to rely upon the Franck–Condon principle and upon difficult measurements of intensities. In polyatomic molecules, however, the situation is reversed. Here the rotational structure is usually not resolved, whereas the intensities of absorption can be measured, especially in solution, with fair accuracy. Thus the Franck–Condon principle in polyatomic molecules has a rôle that it does not have in diatomic ones. Given the intensity distribution in a band system and the elastic constants for the combining states, it allows a non-empirical estimate to be made of the change in molecular dimensions.

Herzberg and Teller (*Z. physikal. Chem.*, 1933, *B*, **21**, 410) first showed how the Franck–Condon principle was to be applied in polyatomic molecules. A change in molecular dimensions may be expressed as a change in the origins of some or all of the normal co-ordinates for nuclear vibrations. Those vibrations whose origins are so diplaced in an electronic transition appear in the spectrum in progressions. Every such vibration behaves as if it belonged to a diatomic molecule whose internuclear separation changed in an electronic transition. On the other hand, vibrations whose origins are not displaced behave as if they belonged to a diatomic molecule in which only the force constant, and not the equilibrium internuclear separation, changed in the transition; such vibrations appear strongly only in zero-quantum changes 0—0, 1—1, etc., and much more weakly in two-quantum changes.

The simplest situation exists when the polyatomic molecule, upon excitation, retains all its elements of symmetry. This is the case if it undergoes a symmetrical expansion or contraction, and the spectrum then shows progressions in the totally symmetrical vibrations alone. The 2600 A. band system of benzene is of this simple type, and the initial and the final state for one band may accordingly be written :

$$\left.\begin{aligned}\Psi(\mathbf{A}_{1g}) &= \phi(\mathbf{A}_{1g})\phi_0(A_{1g})\phi_0(E_g^+)\\ \Psi(\mathbf{B}_{2u}) &= \phi(\mathbf{B}_{2u})\phi_n'(A_{1g})\phi_1'(E_g^+)\end{aligned}\right\} \quad \ldots\ldots\ldots \quad (1)$$

where Ψ stands for a vibrational-electronic wave function, ϕ is a pure electronic wave function, and ϕ_n, ϕ_n' are nth quantum state harmonic oscillator * wave functions in the $\mathbf{A}_{1g}$ and $\mathbf{B}_{2u}$ electronic states respectively. The A_{1g} vibration is the totally symmetrical one, whose quantum number changes along the progressions; while the E_g^+ vibration is one which occurs with one

* Judged from the very slow convergence of successive A_{1g} vibrational levels (Garforth and Ingold, *J.*, 1948, 417) the assumption of harmonic forces is justified, in further contrast to diatomic molecules. The matter is examined in an Appendix.

quantum in the upper state of all the stronger bands of the absorption spectrum, as is noted below. The further but unspecified vibrational wave functions in (1) are to be the same in both states. We discuss the relation between the intensity of absorption associated with particular values of the quantum number n of (1) and the change in ring size between the two electronic states. A comparison with the experimental intensity distribution will then give a value for the size of the benzene ring in the B_{2u} state.

No transitions occur between the wave functions (1) unless, as the most likely possibility, the upper state becomes mixed with the E_1^- electronic state. E_j^+ vibrations may effect the necessary perturbation as follows:

$$\psi^*(B_{2u})\phi_1'(E_j^+) = \psi(B_{2u})\phi_1'(E_j^+) + \delta\psi(E_1^-)\phi_2'(E_j^+) \quad . \quad . \quad . \quad . \quad . \quad (2)$$

ψ^* depends on the nuclear motion as expressed in (2), whereas the unstarred electronic wave functions do not. δ is a small mixing coefficient, and when $\psi^*(B_{2u})$ is used instead of $\psi(B_{2u})$ in (1) the transition moment D_n is:

$$D_n = \int\phi_0(A_{1g})\phi_n'(A_{1g})d\tau_{nucl.} \cdot \delta\int\psi(A_{2g})\Sigma_i ez_i\psi(E_1^-)d\tau_{elec.}$$

$$= k_1\int\phi_0(A_{1g})\phi_n'(A_{1g})d\tau_{nucl.} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

since the second factor is a constant for the whole band system. The intensity of absorption is proportional to $(D_n)^2$. The relative intensity distribution in a band system is governed by the expression

$$I_n = k_2(\nu_n/\nu_0)^4\left[\int\phi_0(A_{1g})\phi_n'(A_{1g})d\tau\right]^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

where ν_n stands for the frequency of a transition ending at the nth quantum state of the A_{1g} vibration and k_2 includes the numerical constants. It is the case that the small Boltzmann factor for the ground-state A_{1g} 992 cm.$^{-1}$ frequency allows attention to be confined to those transitions starting from the zero-quantum state of that vibration. This was implied in (1).

If no change in ring size occurs on excitation, ϕ_0 and ϕ_n' are oscillator wave functions about the same point as origin, and only the integral for $n = 0$ is important (*i.e.*, only the 0–0 band appears strongly). If there is a change in ring size ϕ_0 and ϕ_n' refer to different origins and they overlap over a range of n, the spectral intensity associated with any one n value being given by (4). This is of course simply the expression of the Franck–Condon principle given by Condon (*Physical Rev.*, 1928, **32**, 858) and for polyatomic molecules by Herzberg and Teller (*loc. cit.*). The basic integrals in (4) were worked out by Hutchisson (*loc. cit.*) in forms specially convenient for diatomic molecules and they may be adapted to this case. A simple closed expression, however, becomes applicable when one of the oscillators is always in its lowest state and this will be given.

The mechanics of the low-frequency totally symmetrical vibration of benzene are that the carbon atoms and their attached hydrogen atoms move in phase and with roughly equal amplitudes. It is therefore a very good approximation to this mode of vibration to treat each CH group as a single mass point. The alternative, and superior, calculation is to allow for internal motion in the CH group by working with appropriate normal co-ordinates. The results of these two methods are to be compared, but the detail of the second calculation is reserved for the Appendix. The first and simpler calculation is surprisingly accurate and is alone likely to be manageable for larger molecules. In both cases a further simplification is to suppose the elastic constants to be the same in the upper as in the lower state. As will be shown, even this apparently drastic step introduces only a small error into the result.

The system being supposed to be six CH " atoms " in a regular hexagon, a uniform expansion by a radial distance $q/\sqrt{6}$ moves the origin for the A_{1g} normal co-ordinate by q. We consider therefore two harmonic oscillators whose origins are q apart. These are distinguished by subscripts 1 and 2. Oscillator 1 is to be in its zeroth state (*i.e.*, it is to be the ground electronic state A_{1g} vibration) whereas 2 is to be excited to its nth quantum state.

$$\left.\begin{aligned}\phi_0(\sqrt{\beta_1}x_1) &= \left(\sqrt{\frac{\beta_1}{\pi}}\right)^{\frac{1}{2}} e^{-\beta_1 x_1^2/2} \\ \phi_n'(\sqrt{\beta_2}x_2) &= \left(\sqrt{\frac{\beta_2}{\pi}}/2^n n!\right)^{\frac{1}{2}} H_n(\sqrt{\beta_2}x_2)e^{-\beta_2 x_2^2/2}\end{aligned}\right\} \quad . \quad . \quad . \quad . \quad . \quad (5)$$

The expression $\beta = \frac{2\pi}{h}\sqrt{mk}$ and the H_n are Hermite polynomials. The overlap integral between these two functions, which appears in (3) and (4), may be shown to be:

$$\int \phi_n(\sqrt{\beta_1}x_1)\phi_{n'}(\sqrt{\beta_2}x_2)dx = e^{-\beta_1\delta^2/2(1+\rho)} \sum_r \left(\frac{\sqrt{\beta_2}\delta\rho}{1+\rho}\right)^{n-r} \left\{\frac{n!}{r!(n-r)!}\right\}^{\frac{1}{2}} \left\{\frac{2^{n-r}}{(n-r)!}\right\}^{\frac{1}{2}} S_{2r} \quad . \quad (6)$$

In (6) $\rho = \beta_1/\beta_2$ and the S_{2r} are the elementary overlap integrals between oscillator wave functions about a common origin. These integrals vanish for odd values of r, and for even values are given by

$$S_{2r} = \frac{1}{(r/2)!}\sqrt{\frac{r!}{2^r}}\left(\frac{2\sqrt{\rho}}{1+\rho}\right)^{\frac{1}{2}}\left(\frac{1-\rho}{1+\rho}\right)^{r/2} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

For $\rho = 1$, $S_{00} = 1$ and all others vanish. The values needed for benzene, in which $\rho = \nu_1/\nu_2 = 1{\cdot}075$, are: $S_{00} = 0{\cdot}9997$, $S_{02} = 0{\cdot}0255$, $S_{04} = 7{\cdot}95 \times 10^{-4}$.

A constant multiplier being excluded, (6) together with values of (7) directly give the quantity D_n in terms of β_2, ρ, and q. Used in (4), they give the relative intensity distribution, in terms of the same quantities, between bands of different n. Table I gives sets of relative I_n values for a number of values of q. The approximation is that of CH mass points and the constants that enter are the frequencies $\nu_1 = 992$ cm.$^{-1}$, $\nu_2 = 923$ cm.$^{-1}$, and the isotopic masses C = 12, H = 1·008.

TABLE I.

Calculated relative intensity distributions.

$q/\sqrt{6}$ (A.).	0·0343.	0·0351.	0·0359.	0·0367.	0·0375.
I_0	1	1	1	1	1
I_1	1·38	1·45	1·52	1·59	1·66
I_2	0·90	0·99	1·09	1·20	1·31
I_3	0·37	0·43	0·50	0·57	0·66
I_4	0·11	0·13	0·16	0·20	0·24

Experimentally, the gross features of the intensity distribution are that bands $n = 1$ and $n = 2$ are stronger than $n = 0$, the former ($n = 1$) being considerably stronger and the latter ($n = 2$) stronger by a small margin. Later bands fall rapidly in intensity. This is enough, with use of Table I, to fix the change in equilibrium C–C separation between 0·0351 A. and 0·0376 A. These gross features are apparent in spectra taken in solution, as for example those of Mayneord and Roe (*Proc. Roy. Soc.*, 1935, *A*, **152**, 299). A closer study of the spectra is necessary for precise values of the intensity distribution.

The experimental intensities in most polyatomic molecules must be taken from solution spectra alone, but in benzene the exhaustive analysis and assignments in the vapour spectrum by Garforth, Ingold, and Poole (*J.*, 1948, 406) allow a most valuable check. Indeed, the intensities in the vapour spectrum are to be preferred where an analysis has been made. Broadly, in the vapour spectrum, the intensities of individual bands in a progression may be compared, whereas in solution only the summed intensities of a large number of such members of progressions are available in broad band groups. The former comparison is in principle the better, but is much hampered by the widespread occurrence of intensity transfers between bands by Fermi resonance. Garforth and Ingold (*loc. cit.*, p. 421) have examined a striking case of this and elsewhere brought to light many definite examples. In general, a strong band loses a part of its proper (harmonic approximation) intensity to weaker bands which fall near to it in frequency. Neither the strong nor the weak bands in these alliances furnish material for the comparison of intensities in progressions, because each member of a progression is affected by the proximity of other bands, and by amounts which vary in a very irregular way. Two bands however may perturb one another in this way only if their final states have the same symmetry properties. There is in the assignments of Garforth, Ingold, and Poole (*loc. cit.*) a single long progression which, upon these grounds, is likely to be free from intensity disturbances. All except this one have final states whose vibrational symmetry includes one or all of A_{1g}, A_{2u}, and E_g^+ representations. None of these is useful for the present purpose. The unique progression is denoted by Ingold as the M progression and its transitions start and end at states having one quantum of the E_g^- vibration. The members are given by:

$$\nu = 38090 + E_g^{+\prime} + (E_g^{-\prime} - E_g^-) + p' \, 923 \text{ cm.}^{-1} \; (p' = 0,\ 1,\ 2,\ 3,\ 4).$$

The final states of this progression belong to B_{1u}, B_{2u}, and E_{1}^{-}. There are no other progressions with more than two members whose final states match these, and it follows that intensity transfers must be small. The vapour spectrum intensity distribution given in Table II has been calculated from this progression by using the experimental intensities found by Radle and Beck (*J. Chem. Physics*, 1940, **8**, 507).

In solution, the measurement of intensities as proportional to the area under the extinction curve is not suitable to the present purpose because the area includes a contribution by a continuous absorption which increases towards higher frequencies. This continuous absorption records transitions ending at dissociating molecules. It might properly be regarded as belonging to the band system as a whole but has no reference to particular values of the vibrational quantum numbers. To make the comparison of intensities, therefore, this continuous absorption would have in some way to be subtracted and the remainder analysed. Instead, the solution spectrum values given in Table II are based on the maximum values of extinction coefficients in the distinct band groups in the solution spectrum. These measure the relative areas of the band groups provided the shapes are the same. The effect of the continuous absorption is much less in this measurement because it appears only as a small addition to each maximum, and it might fairly safely be corrected for. Its influence is negligible in the first few maxima and no correction has in fact been made to the figures given in Table II. These have been obtained from the spectrum in alcohol solution given by Mayneord and Roe (*loc. cit.*).

TABLE II.

Experimental relative intensity distributions.

	Vapour spectrum. (Radle and Beck, *loc. cit.*).	Solution spectrum.* (Mayneord and Roe, *loc. cit.*).
I_0	1	1
I_1	1·46	1·45
I_2	1·12	1·12
I_3	0·42	0·65
	0·17	—

* A new experimental study by Mr. I. G. Ross using a Cary Recording Spectrophotometer gives the values: 1, 1·48, 1·18, 0·69. The differences between these figures and those quoted in the table are not significant in the subsequent comparison with Table I.

The best agreements between the experimental values and the calculated ones of Table I are for $q/\sqrt{6}$ not less than 0·0359 A. and not greater than 0·0367 A. Thus in the approximation of CH mass points the increase in the C–C distance in the B_{2u} electronic state is 0·036 A.

When, in the more precise calculations already referred to, account is taken of relative motion within each C–H unit the increase in C–C distance is found to be 0·037 A., and this should be correct to 0·001 A. The calculation is outlined in the Appendix. Here the C and H atoms are allowed to have different motions and the calculation involves two unknown quantities, instead of one as formerly. These are the increase in the C–C distance as before, and the change in the C–H distance. Previously the C–H distance was, in effect, taken as unchanged. Now, however, a value must be assigned to it in order to calculate the change in C–C distance. If the change is taken to be zero, then the refined calculation gives the same result, to within 1%, as the simple one did. The procedure we have adopted is to use a value for the change in C–H bond length deduced by Garforth, Ingold, and Poole (*J.*, 1948, 508) by applying Badger's rule to the observed force constants. This gives a shortening of the C–H bond length by 0·01 A. in the B_{2u} state. With this the Franck–Condon calculation gives the value 0·037 A. for the increase in C–C distance. It will be noticed that the change in calculated C–C distance due to a C–H change of 0·01 A. is 0·001 A.; thus the incorporation of this empirical quantity in the working does not have a critical effect on the accuracy of the result.

The final variation in method is that of supposing the elastic constants in the two electronic states to be the same. Practically, this means that the calculation can be made without any detailed information about the excited state. The starting point is a knowledge of the elastic constants of the ground state, together with the experimental intensity distribution in the spectrum. In benzene the experimental results are now fitted about equally well by values of the C–C increase of 0·0355 A. and 0·0359 A. From this simplest model therefore the result is between 0·035 A. and 0·036 A. It is striking how closely this agrees with the more precise calculations. In more complicated molecules this last method, on its present showing, may be

used with some confidence. The largest single correction to it is likely to be that for the change in equilibrium C–H distance.

Finally, Table III displays values for the increase in C–C distance upon excitation to the B_{2u} state from three different sources. The first is a theoretical value obtained by Kynch and

TABLE III.

Values for the increase in C–C distance in the B_{2u} electronic state.

Theoretical calculation (Kynch and Penney)	0·05 A.	
Badger's rule (Garforth, Ingold, and Poole)	(0·0375 A.) *	2·7%
Douglas Clark's rule (Garforth, Ingold, and Poole)	(0·0361 A.) *	2·6%
Franck–Condon principle	**0·087** A.	
Franck–Condon principle with CH groups as single mass points	0·036 A.	
Same, with elastic constants unaltered in the upper state	0·035—0·036 A.	

* Worked out from the published percentages by using 1·39 A. for the ground state C–C distance.

Penney (*Proc. Roy. Soc.*, **1941**, *A*, **179**, 266) in the electron-pair approximation. The second and third are due to Garforth, Ingold, and Poole (*J.*, 1948, 508) and are based upon empirical relations between force constants and bond lengths. The remainder are Franck–Condon values. The value in heavy type is recommended. The agreement throughout these independent estimates, and especially between those based immediately upon elastic constants and spectral intensities, is satisfactory.

APPENDIX 1.

The Inclusion of Internal C–H *Motion.*—The force constants given by Garforth, Ingold, and Poole (*loc. cit.*, p. 491) being used, the following are the normal co-ordinates for the motion of a single CH group.

Ground electronic state:

$$\left.\begin{aligned}\xi_1 &= 0{\cdot}9503\ p_C + 0{\cdot}3114\ p_H\\ \xi_2 &= 0{\cdot}3114\ p_C - 0{\cdot}9503\ p_H\end{aligned}\right\} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

Excited state:

$$\left.\begin{aligned}\xi_1' &= 0{\cdot}9525\ p_C + 0{\cdot}3046\ p_H\\ \xi_2' &= 0{\cdot}3046\ p_C - 0{\cdot}9525\ p_H\end{aligned}\right\} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

The p's are mass-reduced co-ordinates and the x's displacements:

$$p_C = \sqrt{12/1{\cdot}008}\ x_C$$
$$p_H = x_H$$

The first co-ordinate in each of (8) and (9) is that for the desired low-frequency motion, and when the system is oscillating in this mode $\xi_2(\xi_2') = 0$. Thus in the ground state

$$\left.\begin{aligned}&0{\cdot}3114\ p_C = 0{\cdot}9503\ p_H \text{ and } \xi_1 = 1{\cdot}0523\ p_C = 13{\cdot}1825\ x_C\\ &\text{and in the excited state } \ |\xi_1'| = 1{\cdot}0499\ p_C = 13{\cdot}1225\ x_C\end{aligned}\right\} \quad . \quad . \quad . \quad (10)$$

It will be noticed, in passing, that the hydrogens are displaced about 1·1 times as far as the carbons, and in the same phase, in this mode. The relations (10) show that the motion of the carbon atoms in the actual system is equivalent to the oscillations of mass points of masses 13·1825 and 13·1225, respectively. This enables the work to be linked with that given in the text. The oscillator constants β in the two states are $3{\cdot}908 \times 10^{16}$ (ground) and $3{\cdot}608 \times 10^{16}$ (excited); $\rho = 1{\cdot}0834$. Values for the S_n and of intensity distributions for chosen values of q may be found from these. q now refers directly only to the separation between the origins of normal co-ordinates and not to the actual displacements of the carbon atoms. Table IV gives a few such calculated intensity distributions.

TABLE IV.

q (A.).	0·087.	0·088.	0·089.
I_0	1	1	1
I_1	1·51	1·55	1·58
I_2	1·08	1·13	1·19
I_3	0·49	0·52	0·56
I_4	0·16	0·17	0·19

Here 0·087 A. and 0·088 A. fit the experimental distributions about equally well.

If d is the increase in the C–C distance and f the shortening of the C–H bond, then, a term which is very small for small f being neglected, it may be shown that the relation between q and these quantities is :

$$q \cong \sqrt{6}(0{\cdot}90d - 0{\cdot}084f)$$

Use of this expression gives $d = 0{\cdot}037$ A. for $f = 0{\cdot}01$ A.

Appendix 2.

Anharmonicity in the Vibrations.—If the potential field for the A_{1g} vibrations were strongly anharmonic, the working would become really very complicated. This happens in diatomic molecules such as H_2 (Hutchisson, *loc. cit.*) but is not expected so much in polyatomic molecules. It may be neglected altogether in benzene for reasons now to be given.

Suppose the potential function to contain a cubic and a quartic term as the principal anharmonicities :

$$V(x) = \tfrac{1}{2}kx^2 + ax^3 + bx^4$$

The quartic term has a first-order effect upon the energy levels and we may set an upper limit to it by assuming that it causes the whole of the observed convergence. The anharmonic correction to the seventh quantum state of the A_{1g} vibration is 7 cm.$^{-1}$ (Garforth and Ingold, *J.*, 1948, 417) and by first-order perturbation theory this leads to $b/\beta^4 = 1{\cdot}64 \times 10^{-17}$ dynes cm.$^{-4}$. The fourth-power term causes intensity transfers between a band of a progression and the second and fourth bands on either side of it. The correction to the intensity of a band for $n = 2$, for example, is easily found by first-order perturbation theory to be in the order 10^{-4} for the value of b/β^4 given. Evidently the fourth-power term is negligible.

The cubic term has no first-order effect upon the energy levels but only a second-order one. It is possible to form an upper estimate of the cubic term (an improbably high upper estimate) by supposing the whole of the observed convergence to be due to its second-order effect upon the energy levels. Where there is no first-order term, the second order correction to the energy of the nth state is a sum of contributions from all states joined to it by matrix components of the perturbing potential :

$$W_n = \sum_{m \neq n} \frac{(H_{mn})^2}{\nu_n - \nu_m}; \quad H_{mn} = \frac{a}{\beta^{3/2}} \int \phi_m'(A_{1g}) \beta^{3/2} x^3 \phi_n'(A_{1g}) \mathrm{d}x$$

Four matrix components exist, joining the nth state to states $n \pm 1$ and $n \pm 3$. The higher frequency states depress, and the lower raise, the perturbed state, with the former predominating. Again, by use of the fact that the seventh quantum level is depressed by 7 cm.$^{-1}$ the relations given above lead to $a/\beta^{3/2} \cong 1{\cdot}1 \times 10^{-12}$ dynes cm.$^{-1}$. The magnitude of the intensity transfer due to this may now be calculated. The largest matrix component joins the nth to the $(n + 1)$th state. The coefficient of the $(n + 1)$th wave function in the perturbed nth is :

$$\frac{a/\beta^{3/2} \times 3/(2\sqrt{2}) \times (n+1)^{3/2}}{1{\cdot}835 \times 10^{-15}} \cong 6{\cdot}4 \times 10^{-4}(n+1)^{3/2}$$

For $n = 2$, which is important in the interpretation of the experimental intensities, the coefficient is about $3{\cdot}3 \times 10^{-3}$. The fraction of the intensity transferred is the square of this, and so it may be said that 0·1% is an upper limit to the intensity transfers by anharmonicity in the bands whose intensities are critical. For $n = 5$ the transfer approaches only 1%, which is still negligibly small. The anharmonicity of the A_{1g} potential may therefore be altogether neglected.

My thanks are due to Dr. Edward Teller and to Professor C. K. Ingold, F.R.S., for discussions about this subject. The work has been carried out during tenure of a Turner and Newall Research Fellowship in the University of London.

The Sir William Ramsay and Ralph Forster Laboratories,
University College, London. [*Received, May 1st*, 1950.]

443. *Thermodynamic Factors in Stereo-specific Processes. The Transformation of Diastereoisomers of Brucine 2'-(2-Hydroxy-2-propyl)-diphenyl-2-carboxylic Acid.*

By H. Kacser and A. R. Ubbelohde.

Experiments have been made to assess the thermodynamic factors controlling a stereo-specific reaction, with a view to giving a physico-chemical interpretation to Fischer's lock–key analogy.

The brucine salt of (−)-2'-(2-hydroxy-2-propyl)diphenyl-2-carboxylic acid was prepared and dissolved in chloroform. The rate of mutarotation to the brucine–(+)-acid/brucine–(−)-acid equilibrium mixture was measured over the temperature range 12—43°.

For the reaction, brucine-(+)-acid $\underset{k_L}{\overset{k_D}{\rightleftharpoons}}$ brucine–(−)-acid, the kinetics were substantially unimolecular, with $k_L = 3{\cdot}32 \times 10^{13} \exp(-23{,}200/RT)$, $k_D = 2{\cdot}65 \times 10^{13} \exp(-23{,}200/RT)$, $\Delta H^\circ \approx$ zero, and $\Delta S^\circ \approx 0{\cdot}43$ entropy unit per mole.

These results are discussed in relation to other data. In the lock–key analogy, the difference in "fit" of the (+) and (−) "keys" in the "lock" corresponds with a difference between thermodynamic parameters of the diastereoisomeric complexes. It is suggested that entropy differences play an important and sometimes a predominant part.

Since the original discovery by Pasteur of differences of solubility between (+)–(+) and (+)–(−) salts, a variety of physicochemical processes have been reported which are stereo-specific. All such processes involve an asymmetric "director" and an "acceptor system." They include processes variously described as partial asymmetric synthesis, asymmetric induction, mutarotation, asymmetric transformation of the first and second order, resolution by crystallisation or by adsorption, epimerisation, partial racemisation, and enzyme reactivity. The biological significance of stereo-specific reactions was described, in the case of enzymes, by Emil Fischer's "lock–key" analogy. With simpler systems the "locks" distinguish less completely between the better-fitting key and its optical antipode, but the physical chemistry is more amenable to exact measurement.

The object of the experiments described in this paper was to investigate a system where the stereo-specific process is fairly simple and measurements of kinetics and equilibria would permit an assessment of the relative importance of energy and entropy factors.

The choice of the system to give accurate values of ΔF°, ΔH°, ΔS°, k_L,* and k_D* was governed by the need for reliable purity, simple kinetics, and accurate measurements of concentration changes.

Brucine 2'-(2-hydroxy-2-propyl)diphenyl-2-carboxylic acid (Corbellini and Angeletti, *Atti R. Accad. Lincei*, 1932, **15**, 968; Jamison and Turner, *J.*, 1942, 437) appeared to satisfy these conditions. Certain disadvantages attaching to this compound became evident as the work proceeded (cf. Experimental section) and were responsible for the fact that the values of the kinetic parameters k and E could be determined with substantially higher accuracy than the thermodynamic parameters ΔF°, ΔH°, and ΔS°.

The general procedure was to prepare the brucine (−)-salt by asymmetric transformation of the second order, by evaporating a chloroform solution containing equimolecular quantities of brucine and the (±)-mixture of acids. This salt was then made up to volume in chloroform solution and transferred to a micro-polarimeter, a jacketed thermostat being used. Polarimetric determinations of the molecular rotation were made at intervals, with filtered monochromatic radiation with the green 5461 and the yellow 5893 line from mercury and sodium lamps. These measurements gave values of reaction rates. By using additional data on the brucine –(±)-acid mixture, equilibrium constants could be evaluated at a range of temperatures.

Experimental.

Polarimetric Measurements.—The micropolarimeter tube used has been described elsewhere (Kacser and Ubbelohde, *J. Soc. Chem. Ind.*, 1949, **68**, 135). Water pumped from a thermostat maintained the tube at 11·8°, 21·3°, 29·1°, 35·4° and 43·1°, normally within ± 0·05°, and within ±0·2° at the lowest temperature. Temperatures lower than 11·8° were used in a limited range of experiments, but gave very slow mutarotation. With temperatures substantially higher than 43·1° the rate was considered too fast to give readings of sufficient accuracy.

Preparation of Materials.—Brucine. The highly specific nature of asymmetric reactions made it essential to have only one molecular species present as "director." For this purpose pure brucine was

* The suffixes L and D refer to the (−)- and (+)-substances and have not the specific significance now attaching to these small capital letters in other aspects of stereochemistry.

prepared as described elsewhere. It had m. p. 179·2°, $[\alpha]_{5461}^{20}$ −149·5° and $[\alpha]_{5893}^{20}$ −120·5° (*c* = 1 g. in 100 ml. of pure dry chloroform).

2'-(2-Hydroxy-2-propyl)diphenyl-2-carboxylic acid was prepared according to the methods previously described (Corbellini and Angeletti, and Jamison and Turner, *loc. cit.*). The acid could be converted nearly quantitatively into the lactone (m. p. 123°) by repeated crystallisation from hot alcohol. Benzene retarded this change. Purification of the acid was finally effected by slow evaporation of the cold benzene solution.

The m. p. (136·5—137°) was rather sensitive to the rate of heating as the crystals lost water when kept at high temperatures.

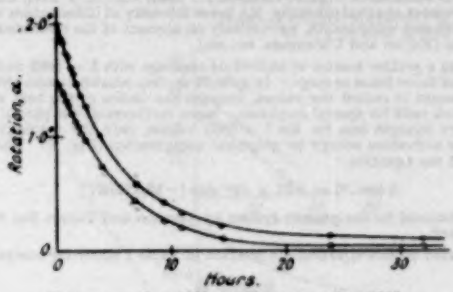
The brucine (−)-salt was prepared as described previously.

Reaction Kinetics.—Each isothermal mutarotation was observed according to the following procedure.

Approx. 0·18 g. of the salt was accurately weighed into a calibrated 5-ml. flask, which was placed in a thermostat and made up to volume with chloroform previously warmed to the desired temperature. The solution was transferred to the micropolarimeter by using methods previously described (Kacser and Ubbelohde, *loc. cit.*).

FIG. 1.

Change of rotation of brucine (−)-salt in chloroform solution at 35·4°.



Upper curve, λ = 5461 A.; *lower curve,* λ = 5893 A.

The course of the observations may be illustrated by Fig. 1 which gives the results at 35·4°. Values of α were determined at intervals, for each of the two wave-lengths, merely by changing the illumination.

For the unimolecular change

$$\text{brucine (}-\text{)-salt} \underset{k_D}{\overset{k_L}{\rightleftharpoons}} \text{brucine (}+\text{)-salt} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$k = k_L + k_D = \frac{1}{t} \ln [(\alpha_0 - \alpha_\infty)/(\alpha_t - \alpha_\infty)]$$

where α_0, α_t and α_∞ are the molecular rotations at times 0, *t* and at equilibrium.

It was verified, by calculating a series of values of *k* for the extrapolated values of α_0 and α_∞, that the reaction was of the first order.

A set of *k* values is given below, as illustration (this corresponds with the plot Fig. 1):

$$\alpha_0 = 2{\cdot}00; \quad \alpha_\infty = 0{\cdot}09; \quad \theta = 35{\cdot}4; \quad \lambda = 5461.$$

t, hours.	*k*, hours^{-1}.	*t*.	*k*.	*t*.	*k*.
0·37	0·083	1·30	0·077	3·83	0·083
0·48	0·075	1·57	0·074	7·00	0·082
0·65	0·068	1·83	0·081	9·37	0·083
0·87	0·072	2·16	0·082	10·93	0·083
1·07	0·068	2·62	0·077	14·37	0·081
				22·83	0·074

In calculating rate constants it is however preferable to avoid using the molecular rotations α_0 and α_∞ which can only be determined by extrapolation and are subject to certain systematic as well as random errors. The procedure proposed by Guggenheim (*Phil. Mag.*, 1926, **2**, 538) was followed by taking pairs of readings α_t and $\alpha_{t+\tau}$ where τ is any convenient fixed interval. For unimolecular processes a plot of $\log_{10}(\alpha_t - \alpha_{t+\tau})$ against *t* should give a straight line with slope $-k \log_{10} e$. Actually *k* was computed by calculating lines of closest fit, taking pairs of values of α_t and $\alpha_{t+\tau}$ from a smooth curve drawn through the direct observations. These calculations also yielded values of α_0 and α_∞. Standard deviations are tabulated in Table I which gives the values of *k* thus obtained. Table II gives the values of $[\alpha_L]$ (from α_0) for the pure brucine (−)-salt and $[\alpha_E]$ (from α_∞) for the equilibrium mixture respectively. The values of $[\alpha_{DL}]$ in Table II were calculated as below.

TABLE I.

Velocity Constants.

	$k' = k \times 10^{-2}$ hours^{-1}.		
	k', obs.	k', obs.	k', calc., eqn. (2).
θ.	$\lambda = 5893$.	$\lambda = 5461$.	
11·8°	$0{\cdot}49_4 \pm 0{\cdot}0046$	$0{\cdot}33_4 \pm 0{\cdot}0012$	$0{\cdot}35_4$
21·3	$1{\cdot}60_4 \pm 0{\cdot}010$	$1{\cdot}36_4 \pm 0{\cdot}013$	$1{\cdot}33_6$
29·1	$3{\cdot}73_4 \pm 0{\cdot}110$	$3{\cdot}68_4 \pm 0{\cdot}035$	$3{\cdot}70_6$
35·4	$7{\cdot}99_6 \pm 0{\cdot}109$	$8{\cdot}10_6 \pm 0{\cdot}050$	$8{\cdot}13_7$
43·1	$22{\cdot}15_6 \pm 0{\cdot}208$	$21{\cdot}65_7 \pm 0{\cdot}119$	$20{\cdot}44$

The values given in Table I record random deviations from the unimolecular constants as calculated by standard-error theory. There are reasons for suspecting a systematic bias in the readings with $\lambda = 5893$. In kinetic measurements, rates of adaptation to scotopic vision are important. At equal intensities the rates are less favourable for $\lambda = 5893$ than for $\lambda = 5461$ by a factor of the order of 10 (H. Hartridge, "Recent Advances in the Physiology of Vision," Churchill, 1950). Other factors for which the yellow wave-length is also less favourable are subjective luminosities (*op. cit.*, p. 43; also Weissberger, "Physical Methods of Organic Chemistry," 1946, Vol. II, p. 910), hue discrimination, etc. Apart from these differences at equal intensity, the lower intensity of illumination with $\lambda = 5893$ further handicaps readings with this wave-length, particularly on account of the restricted field available in the micro-polarimeter tube (Kaeser and Ubbelohde, *loc. cit.*).

Generally there was a greater scatter in individual readings with $\lambda = 5893$ than with $\lambda = 5461$, the spread being sometimes three times as large. In spite of the less reliable results obtained with $\lambda = 5893$, it is considered of interest to record the values, because the choice of the best wave-length to obtain accuracy in optical work calls for special emphasis. Since furthermore the plot of log k against $1/T$ did not give a satisfactory straight line for the $\lambda = 5893$ values, only the readings with $\lambda = 5461$ were used to determine the activation energy by graphical computation (Fig. 2). These gave $E = 23{\cdot}2 \pm 0{\cdot}8$ kcals./g.-mole with the equation :

$$k \text{ (sec.}^{-1}) = 5{\cdot}97 \times 10^{11} \exp(-23{,}200/RT) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

The single result obtained for the present system by Jamison and Turner (*loc. cit.*) is shown in Fig. 2 and is in good agreement.

Values of k' calculated by this equation are inserted in Table I above for comparison.

TABLE II.

Extrapolated values of specific rotations.

Temp.	Concn., mg./ml.	λ.	$[\alpha_L]$.	$[\alpha_R]$.	$[\alpha_{DL}]$.*
21·3°	$35{\cdot}9_4$	5461	−48·0°	+0·71°	−4·5°
		5893	−38·3	+2·08	−2·6
29·1	35·8	5461	−47·3	−0·78	−5·3
		5893	−37·4	+0·19	−3·2
35·4	$35{\cdot}5_3$	5461	−46·7	−1·86	−6·0
		5893	−36·8	±0·00	−3·8
43·1	35·9	5461	−46·0	−1·67	−6·5
		5893	−36·2	−0·69	−4·4

* Interpolated values from separate sets of determinations, see below.

The relative amounts of brucine (+)-salt and brucine (−)-salt at equilibrium in equation (1) can be readily calculated if values are also available for the rotation of the pure brucine (+)-salt. Experiments to determine these auxiliary data were made by mixing solutions of brucine in chloroform with the appropriate solutions of the (±)-acid mixture and evaluating

$$[\alpha_{DL}] = \tfrac{1}{2}([\alpha_R] + [\alpha_L]) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

from which and from the values of $[\alpha_L]$ the values of $[\alpha_R]$ could be determined.

Various practical difficulties prevented any very accurate evaluation of the equilibrium constants by this means. These included

(i) The high temperature coefficient of rotation

(ii) Uncertainties in the value $[\alpha_{DL}]$, which has to be determined from the change $\alpha_{DL} \longrightarrow \alpha_\infty$ by extrapolating to $t = 0$.

(iii) Abnormal rotation–time curves for the brucine (±)-mixture, which show a small but definite maximum on the early part of the curve (Figs. 3*a* and 3*b*). This indicates that the kinetics of the change

$$\text{brucine (±)-mixture} \rightleftharpoons \text{equilibrium mixture} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

are not straightforward.

From the numerical calculations, the results of which are quoted above, and from the fact that the (−)-salt could be obtained pure by crystallisation, it is concluded that the kinetics of the change (−)-salt $\rightleftharpoons$ equilibrium are of the first order. There is no evidence of any complications. The

kinetics of the process (±)-salt ⇌ equilibrium are experimentally much less easy to establish. Written out in full detail, the process under observation is :

$$\underset{\text{(solid)}}{(\pm)\text{-Acid}} + \underset{\text{(solid)}}{\text{Brucine}} + \text{Solvent} \xrightarrow{(1)} \underset{\text{(solution)}}{(\pm)\text{-Acid}} + \underset{\text{(solution)}}{\text{Brucine}}$$

$$\downarrow (2)$$

$$\text{Equilibrium solution} \overset{(3)}{\rightleftharpoons} \text{Brucine } (\pm)\text{-salt solution}$$

The kinetic parameters required can only be ascertained from such a system if step 3 predominates substantially to 100%. Further difficulties such as lactone formation or bimolecular ester formation which can arise in parallel with steps (1) and (2) are absent when the starting material is the crystalline (−)-salt. For these reasons no use of the observations on this reaction sequence is made in the kinetic calculations.

FIG. 2.

Temperature coefficient of reaction velocity.

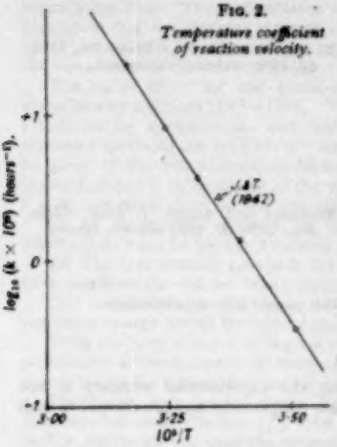
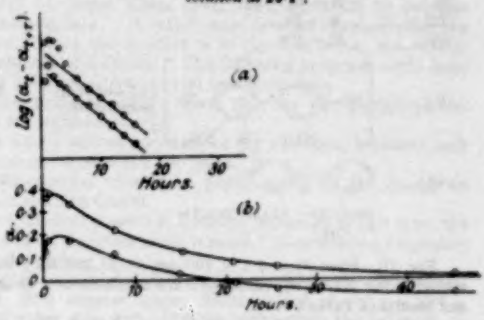


FIG. 3.

Change of rotation of brucine (±)-salt in chloroform solution at 29·1°.



From the logarithmic (Guggenheim) plot it is however evident (Fig. 3*a*) that the course of the reaction after a short time assumes substantially the same slope as for the a_t/t plot at the appropriate temperature. The value of $[a_{pt}]$ was therefore obtained by extrapolating the steady curve at $t = 15{\cdot}5°$ back to $t = 0$.

In order to obtain $[a_{pt}]$ values at other temperatures, consistent with this extrapolated value, the jacket temperature of the polarimeter was changed abruptly in special experiments, after the steady rate of change had been reached. From the change in a, the temperature coefficient of $[a_{pt}]$ was assessed as in Table II. Allowance was made for the thermal expansion of the solution.

From these values, average equilibrium constants

$$K_\theta = ([a_{1t}]_\theta - [a_\infty]_\theta)/([a_\infty]_\theta - [a_{1t}]_\theta - 2[a_{pt}]_\theta)$$

and standard free energy changes for reaction (1) have been calculated as in Table III.

TABLE III.

Equilibrium constants.

Temp.	21·3°	29·1°	35·4°	43·1°
$K_{\text{cale.}}$	1·27₆	1·24₁	1·22₂	1·27₇
$K_{\text{calc.}}$	1·26₆	1·22₁	1·22₂	1·22₇
Mean	1·27₁	1·23₁	1·22₂	1·25₂
$\Delta F°$, cals. g./mole	−140·4	−124·8	−125·0	−141·4

In view of the experimental errors it seems safest to note the fact that the above values of $\Delta F°$ imply that $\Delta H°$ must obviously be very small, and to take the mean value of K over the temperature range:

$$K = 1{\cdot}245 \pm 0{\cdot}025$$
$$\Delta F° = -133 \pm 15 \text{ cals./g.-mol.}$$
$$\Delta H° \approx \text{zero}$$

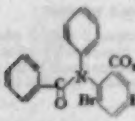
whence $\Delta S° \approx 0{\cdot}43$ cals./g.-mole/degree. The combination of these values with that for $k = k_L + k_D$ gives

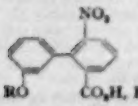
$$k_L = 3{\cdot}32 \times 10^{11} \exp(-23{,}200/RT)$$
$$k_D = 2{\cdot}65 \times 10^{11} \exp(-23{,}200/RT)$$

Discussion.

Comparison of Kinetic Results with Cognate Data.—No data are available for comparison, which cover quite the same range of information. By recalculation of certain published velocity constants partial comparisons can be grouped as follows:

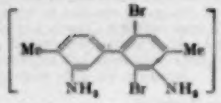
(a) ***Rate constants for the mutarotation of diastereoisomers.***

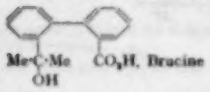
(I.)  Cinchonidine — Jamison and Turner, *J.*, 1938, 1649; solvent, chloroform.



(II.) R = Me.
(III.) R = Et.
(IV.) R = Pr^{n}.

Brucine — Li and Adams, *J. Amer. Chem. Soc.*, 1935, **57**, 1565; solvent, chloroform.

(V.)  (+)-camphorsulphonate. — Patterson and Adams, *J. Amer. Chem. Soc.*, 1935, **57**, 762; solvent, ethanol.

(VI.)  Brucine — This paper; solvent, chloroform.

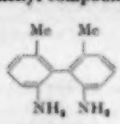
For (I), k(sec.$^{-1}$) $= 3{\cdot}1 \times 10^{10} \exp(-21{,}200/RT)$ but the experimental accuracy is not stated. For (II)—(V), values of k are available only at one temperature and are compared with our results in Table IV.

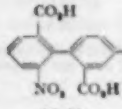
Table IV.

Velocity constants, $k = k_1 + k_2$.

Compound.	Temp.	$k \times 10^4$, hours^{-1}.	Compound.	Temp.	$k \times 10^4$, hours^{-1}.
(II)	24—25°	12·9$_6$	(V)	27°	0·2$_6$
(III)	24—25	2·8$_5$	(VI)	24·5	1·9$_4$
(IV)	24—25	2·1$_4$			

(b) ***Comparison of values of*** **A** ***and*** **E.** No values for diastereoisomeric species of diphenyl derivatives appear to have been previously determined. Data are however available for a number of diphenyl compounds liberated from their resolving agents, as shown in Table V.

(VII.)  — Kistiakowsky and Smith, *J. Amer. Chem. Soc.*, 1936, **58**, 1043.

(VIII.)  — Kuhn and Albrecht, *Annalen*, 1927, **455**, 272.

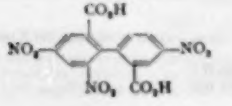
(IX.)  — Kuhn and Albrecht, *Annalen*, 1927, **455**, 221.

TABLE V.

Compound.	$A \times 10^{-11}$.	E, kcals./g.-mole.	Compound.	$A \times 10^{-11}$.	E, kcals./g.-mole.
(VII) (solution) [1] ...	0·83	45·1	(II), (III), and (IV) [2]	1·0—10	21·0
(gas)	0·24	45·1	(VI)	5·97	23·2
(VIII)	7·6	26·6			
(IX)	0·0083	22·4			

[1] The authors state they cannot discriminate between a difference in A and a difference in E on changing from solution to gas. [2] Free acids.

So far as the values of E are concerned, it will be apparent that the compound now investigated encounters obstacles to inversion which are overcome by much the same activation energy as in other diphenyl compounds with only three substituents in the *ortho*-positions to the internuclear link. This is significant in suggesting that the additional brucine molecule in our compound does not obstruct rotation about the internuclear link to any great extent. Jamison and Turner (1942, *loc. cit.*) similarly report that the racemisation rate of the liberated acid is of the same order as the transformation rate of the brucine salt.

The value of A for our stereo-specific reaction falls below the value "normal" for unimolecular reactions (10^{13}—10^{14}). Values of $A \approx 10^{11}$ for this type of compound have been attributed by Kistiakowsky and Smith (*J. Amer. Chem. Soc.*, 1936, **58**, 1043) to reaction processes involving the rotation of "heavy groups." A rather more detailed interpretation can be given of the low probability factor. Since the reaction is of the first order, the rate of transformation is independent of the number of collisions. The following processes could have a large numerical effect on the time lag between activation and transformation.

(i) An appropriate fraction of the collision energy must flow to the phenyl–phenyl internuclear bond to become available as rotational energy.

(ii) The four obstacle groups in the *ortho*-positions may assume (by vibration) locations such as to minimise the van der Waals repulsions between the two pairs.

(iii) A considerable electronic reorganisation must take place, owing to the change in resonance energy whilst the internuclear rotation occurs.

With the large number of degrees of freedom present in complex molecules of this type, the probability of these conditions being satisfied simultaneously is small. Deactivation frequently occurs before the transformation can take place.

Writing p, o, s for the phase factor, orientation factor, and steric factor respectively, Hinshelwood and Winkler (*J.*, 1936, 371) suggest upper limits $P = p \times o \times s = 10^{-2} \times 10^{-2} \times 10^{-1} = 10^{-5}$ so that the present value $P = 10^{-4}$—10^{-5} lies well within the range to be expected on the above interpretation.

Thermodynamic Factors in Stereo-specific Reactions.—(a) *The equilibrium constant.* In a number of equilibria between diastereoisomers values of K range between 1 (*i.e.*, no stereo-specific effect) and about 2. It is convenient to represent all the K values as greater than unity even when the authors represent the inverse ratio, since it is arbitrary which diastereoisomer is selected as product in a reversible reaction. Such values are shown in Table VI.

TABLE VI.

Thermodynamic factors in stereo-specific equilibria.

Compound.	Temp.	K.	$\Delta F°$, cals./g.-mole.	$\Delta H°$, cals./g.-mole.	$\Delta S°$, e.u.	Ref.
(VI)	21—43°	$1{\cdot}24_5$	−133	0	+0·43	1
(I)	18	$1{\cdot}03_5$	—	—	—	2
Mannose	25	1·51	−250	0	+0·84	3
Lactose	25	1·65	−300	+710	+3·4	3
Glucose	25	1·74	−330	0	+1·10	3
Xylose	25	1·86	−370	−550	−0·61	3
(X)	?	1·43	—	—	—	4
(XI)	?	1·11	—	—	—	4
(XII)	?	1·28	—	—	—	5

References: 1 Present work. 2, Jamison and Turner, 1942, *loc. cit.* 3, Kendrew and Moelwyn-Hughes, *Proc. Roy. Soc.*, 1940, *A*, **176**, 352. 4, McKenzie and Smith, *J.*, 1924, **125**, 1582; (X) (−)-menthyl (±)-phenylchloroacetate; (XI) (−)-menthyl (±)-phenylbromoacetate. 5, *Idem*, *Ber.*, 1925, **58**, 894; (XII) (−)-bornyl (±)-phenylchloroacetate.

In spite of the inherent uncertainties arising from rotational analysis, the values of K do not lie very far from unity.

This limitation in the range of K may to some extent be determined by the fact that only systems with K not very different from unity are convenient for experimental study. But owing to the logarithmic form of the relationship $RT \ln K = \Delta F°$ it is clear that at least for the cases of stereo-specific action so far studied the free energy differences are small and do not exceed nRT where n is a small number.

(b) *Values of* $\Delta H°$. The information about $\Delta H°$ is even more limited at present. Apart from the value now obtained, only certain sugars have been studied. Kendrew and Moelwyn-Hughes (*loc. cit.*) consider that in two cases the uncertainties arising from the temperature coefficient of molecular rotations do not exclude $\Delta H° \approx 0$. $\Delta H°$ is in any case of the same order as RT.

(c) *Values of* $\Delta S°$. The values of $\Delta S°$ listed for the sugars are of the same order as that obtained for the present compound. It appears reasonable that the orientation of one part of a molecule with respect to another should be associated with entropy differences of this order. For example, the brucine molecule appears to exert only a rather indirect influence on the two arrangements of the diphenyl derivative in our present investigation, possibly by "blocking out" more of the phase space available for one diastereoisomer than for the other.

Tentative Interpretation of the Lock and Key Mechanism.—Though many more precise studies of stereo-specific reactions are clearly required before the lock–key mechanism can be elucidated fully, especially for cases of biological importance, the order of magnitude of the thermodynamic factors so far observed is significant. Any energy differences between diastereoisomers may quite generally prove to be not large compared with RT. This would in any case be expected from the type of physicochemical interactions which are responsible for the energy differences. Normally these arise only from attractions and repulsions between chemically saturated atoms.

This can give entropy differences between diastereoisomers an important and sometimes a predominating part in controlling stereo-specific reactions. It is not difficult to see how, even when $\Delta H°$ is small, appreciable entropy differences can arise, since the potential energy curves for the two diastereoisomers, as different parts of the structure undergo relative movement, can have practically the same minima but very different shapes at somewhat higher energies, owing to the configurational difference. This would mean that the phase space effectively occupied by the two diastereoisomers may be very different, at any rate at ordinary temperatures.

On this basis the "lock–key" mechanism has a statistical interpretation in which the preferred direction of reaction may be controlled predominantly by differences of probability or entropy.

The Queen's University, Belfast. [*Received, January* 30th, 1950.]

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444. *Search for New Analgesics. Part IV. Variations in the Basic Side-chain of Amidone.*

By P. Ofner and E. Walton.

With a Note on Some Pharmacological Results. By A. F. Green and A. C. White.

Ketones of types (I), (II), (XI), (XII), (XIII), and (XIV) (R being Alk·CO) have been prepared and, where necessary, their structures determined by established methods. Compounds bearing propionyl and 2-dialkylaminopropyl side-chains show maximal analgesic activity. The dibasic compounds (XVI and XVII; R = H) were obtained by reduction of the corresponding cyanides, but neither they nor their acetyl derivatives showed appreciable analgesic acitvity.

In Part III (*J.*, 1949, 648) several series of amidone analogues having considerable variations in the ketonic side-chain were described; those carrying a propionyl group showed maximal analgesic activity. In the work now described the emphasis has therefore been on varying the basic rather than the ketonic side-chain.

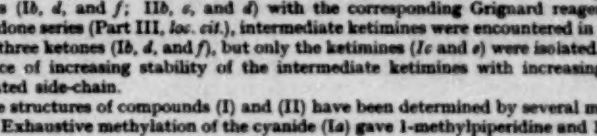
(*a*) *2-Piperidinopropyl Series.*—A mixture of cyanides (I*a*) and (II*a*) was prepared by sodamide alkylation of diphenylmethyl cyanide with 2-chloro-1-piperidinopropane. At first only one of these cyanides (I*a*) was obtained but more recently both have been isolated (*Nature*,

(I.) R·CPh$_2$·CHMe·CH$_2$·N$<$C$_5$H$_{10}$		(II). R·CPh$_2$·CH$_2$·CHMe·N$<$C$_5$H$_{10}$	
(*a*) R = CN	(*d*) R = COEt	(*a*) R = CN	(*d*) R = COPr
(*b*) R = COMe	(*e*) R = CPr:NH	(*b*) R = COMe	(*e*) R = CO·NH$_2$
(*c*) R = CEt:NH	(*f*) R = COPr	(*c*) R = COEt	(*f*) R = H

1949, **163**, 479) by methods described in the Experimental section. Each gave a series of ketones (I*b*, *d*, and *f*; II*b*, *e*, and *d*) with the corresponding Grignard reagents. As in the *iso*amidone series (Part III, *loc. cit.*), intermediate ketimines were encountered in the preparation of the three ketones (I*b*, *d*, and *f*), but only the ketimines (I*e* and *e*) were isolated. There is thus evidence of increasing stability of the intermediate ketimines with increasing length of the associated side-chain.

The structures of compounds (I) and (II) have been determined by several methods.

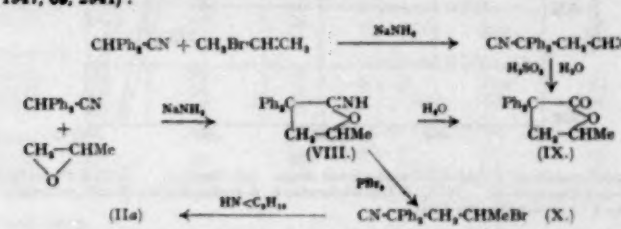
(i) Exhaustive methylation of the cyanide (I*a*) gave 1-methylpiperidine and 1 : 1-diphenyl-2-methylallyl cyanide (III), together with some 1 : 1-diphenyl-2-methylallylformamide (IV). The cyanide (III) was reduced to the primary amine (V) which was found to be identical with that



obtained by reduction of 1 : 1-diphenyl*iso*butyl cyanide (VI) (cf. *Nature*, 1949, **163**, 479; Schultz, Robb, and Sprague, *J. Amer. Chem. Soc.*, 1947, **69**, 2454).

(ii) The structure of the isomeric series (II) was confirmed by sodamide degradation of the cyanide (II*a*) and by hydrolysis of the ketone (II*c*) to give in both cases 3-piperidino-1 : 1-diphenylbutane (II*f*), which was identical with a specimen obtained by Dr. D. W. Adamson by an unambiguous method (cf. *J.*, 1949, S144). Attempts to prepare the butane (II*f*) by hydrolysis of the cyanide (II*a*) yielded only the corresponding amide (II*e*), which could not be further hydrolysed.

(iii) In addition the cyanide (II*a*) was synthesised from diphenylmethyl cyanide and propylene oxide by the unambiguous route described by Easton, Gardner, and Stevens (*J. Amer. Chem. Soc.*, 1947, **69**, 2941):



In this synthesis, proof of the structure of (II*a*) was afforded by hydrolysis of the imino-tetrahydrofuran (VIII) to the lactone (IX), which was in turn obtained by condensation of diphenylmethyl cyanide and allyl bromide as shown in the scheme.

Structural proofs (i), (ii), and (iii) thus determined the positions of the branch methyl groups in the compounds of types (I) and (II).

In contrast with the results of Easton *et al.* (*J. Amer. Chem. Soc.*, 1948, **70**, 76) who claimed to have obtained a third isomer of amidone, no such isomer was found during the working up of any other tertiary aminopropyl series. 4-Piperidino-1 : 1-diphenylbutyl cyanide (XI*a*) in particular might have been produced during the formation of the mixture of cyanides (I*a* and II*a*) by way of 3-piperidinopropylene, which in turn could have been formed by elimination of hydrogen chloride from 2-chloro-1-piperidinopropane. This possibility was, however, considered ruled out by the work described below.

(*b*) *3-Piperidinopropyl Series.*—The cyanide (XI*a*) was obtained from diphenylmethyl cyanide and 1-chloro-3-piperidinopropane [itself prepared from 3-piperidinopropan-1-ol (Hromatka, *Ber.*, 1942, **75***B*, 131)]; its hydrochloride was a well-defined crystalline compound different from those of cyanides (I*a*) and (II*a*). From it the corresponding acetyl, propionyl,

and n-butyryl derivatives (XI*b*, *c*, and *d*) were readily obtained without the production of stable ketimines (cf. however, Easton *et al.*, *J. Amer. Chem. Soc.*, 1948, **70**, 76).

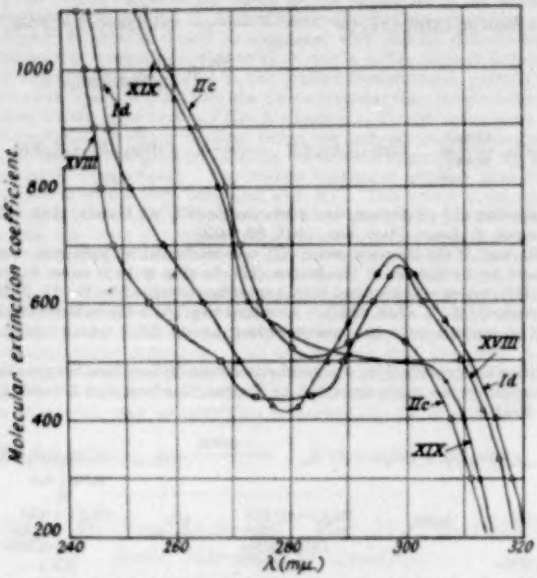
(XI.) R·CPh$_2$·CH$_2$·CH$_2$·CH$_2$·N<C$_5$H$_{10}$

(*a*) R = CN
(*b*) R = COMe
(*c*) R = COEt
(*d*) R = COPr

(XII.) R·CPh$_2$·CH$_2$·CH$_2$·NEt$_2$

(*a*) R = CN
(*b*) R = COEt
(*c*) R = CO·NH$_2$
(*d*) R = CO$_2$H
(*e*) R = CO$_2$Et
(*f*) R = H

(*c*) *2-Diethylaminoethyl Series.*—Earlier in this investigation several members of a 2-diethylaminoethyl series (XII*a*, *b*, *c*, *d*, *e*, and *f*) were prepared (cf. Part III, *loc. cit.*, and Dupré *et al.*, *J.*, 1949, 500), but further work on other 2-dialkylaminoethyl series * was abandoned when it



(XVIII) 6-*Dimethylamino*-4 : 4-*diphenyl*-5-*methylhexan*-3-*one* (iso*Amidone*). (I*d*) 6-*Piperidino*-4 : 4-*diphenyl*-5-*methylhexan*-3-*one*. (XIX) 6-*Dimethylamino*-4 : 4-*diphenylheptan*-3-*one* (*Amidone*). (II*c*) 6-*Piperidino*-4 : 4-*diphenylheptan*-3-*one*.

became apparent that the 2-dialkylaminopropyl side-chain was more effective in the development of analgesic activity.

R·CPh$_2$·CHMe·CH$_2$·NEt$_2$ (XIII.)

(*a*) R = CN
(*b*) R = CEt:NH
(*c*) R = COEt

R·CPh$_2$·CH$_2$·CHMe·NEt$_2$ (XIV.)

(*a*) R = CN
(*b*) R = COEt

CH$_2$:CH·CH$_2$·CPh$_2$·CO·NH$_2$ (XV.)

(*d*) *2-Diethylaminopropyl Series.*—The isomeric cyanides (XIII*a* and XIV*a*) were prepared from 2-chloro-1-diethylaminopropane and diphenylmethyl cyanide, and were separated from each other by taking advantage of the differing solubilities of their hydrochlorides in alcohol. Their structures were determined by exhaustive methylation. The methiodide of (XIII*a*) yielded the cyanide (III), whilst the methiodide of (XIV*a*) gave αα-diphenyl-β-vinylpropionamide (XV) and the lactone (IX) as degradation products (Schultz, Robb, and Sprague, *loc. cit.*).

With ethylmagnesium bromide the cyanide (XIII*a*) formed the ketimine (XIII*b*), which by

* A few other intermediates of this type are described in the Experimental Section.

hydrolysis was converted into the ketone (XIIIc). On the other hand, only the ketone (XIVb) was isolated on similar treatment of the cyanide (XIVa).

It is of interest to note that in both the 2-piperidino- and 2-diethylamino-propyl series, the halide salts of the *iso*-compounds (Ia) and (XIIIa), owing to their higher melting points and lower solubilities, were more readily isolated than the corresponding salts in the normal series (IIa) and (XIVa), whereas the reverse was the case in the original amidone series.

(*e*) *Miscellaneous Amidone Derivatives.*—Reduction of the cyanide precursors of amidone and *iso*amidone (Part III, *loc. cit.*) gave 1-amino-4-dimethylamino-2 : 2-diphenylpentane (XVI; R = H) and 1-amino-4-dimethylamino-2 : 2-diphenyl-3-methylbutane (XVII; R = H), from which the 1-acetamido- (XVI and XVII; R = COMe) and 1-phenylureido- (XVI; R = CO·NHPh) derivatives were prepared. No further work of this type is planned, as a number of similar derivatives have recently been described (*e.g.*, May and Mosettig, *J. Org. Chem.*, 1948, **13**, 459; Cheney *et al.*, *J. Amer. Chem. Soc.*, 1949, **71**, 53, 57).

$NHR{\cdot}CH_2{\cdot}CPh_2{\cdot}CH_2{\cdot}CHMe{\cdot}NMe_2$ (XVI.)

$NHR{\cdot}CH_2{\cdot}CPh_2{\cdot}CHMe{\cdot}CH_2{\cdot}NMe_2$ (XVII.)

The authors are indebted to Dr. T. S. G. Jones for the ultra-violet absorption curves (shown in the figure) of pairs of isomeric ketones in two different dialkylaminopropyl series. It will be seen that these curves bear out the isomeric structures assigned to these ketones on the chemical evidence.

Pharmacological Results.—Several of the compounds described above were tested for analgesic activity in the rat and the results are summarised in the following table.

Pharmacological results.

	Salt.	Approx. analgesic activity (morphine = 1).	Approx. L.D. 50, I.V., mice, mg./kg.
Compound (I).			
R = COMe	HNO_3	0·2	20
CEt:NH	2HCl	nil	20
COEt	HBr	1·0	25
CPr:NH	2HBr	nil	40
COPr	HBr	0·25	30
Compound (II).			
R = COMe	HCl	0·2	15
COEt	HCl	2·4	15
COPr	HNO_3	nil	30
Compound (XI).			
R = COMe	H_2SO_4	nil	45
COEt	HBr	nil	40
COPr	H_2SO_4	nil	40
Compound (XII).			
R = COEt	HBr	0·1	30
Compound (XIII).			
R = CEt:NH	2HCl	nil	12
COEt	HBr	0·6	25
Compound (XIV).			
R = COEt	HBr	1·0	25
Compound (XVI).			
R = H	Base	nil	60
COMe	HBr	nil	80
Compound (XVII).			
R = H	HBr	nil	100
COMe	HBr	nil	110

(Activities less than 0·05 are described as nil.)

From these results it will be seen that :

(*a*) methyl branching in the basic side-chain, particularly in the β-position to the quaternary carbon atom, is an important factor in the development of analgesic activity;

(*b*) small variations in the basic group itself have a relatively minor effect;

(*c*) propionyl derivatives show maximal activity;

(*d*) the ketimines are inactive and apparently do not readily hydrolyse *in vivo* to give the active ketones;

(*e*) the dibasic compounds (XVI and XVII) are virtually inactive.

It should be noted that the above analgesic ratios will not necessarily be the same in other species. In the dog, for example, the ethyl ketones of types (II) and (XIV) have about half the activity of morphine, and the ethyl ketones of (I) and (XIII) have only a fifth to a tenth of the activity of morphine.

Experimental.

(M. p.s are uncorrected.)

3-Piperidino-1 : 1-diphenyl-2-methyl-n-propyl Cyanide (Ia) *and 3-Piperidino-1 : 1-diphenyl-n-butyl Cyanide* (IIa).—These two compounds have recently been mentioned (*Nature*, 1949, **163**, 479; Bockmühl

and Ehrhart, *Annalen*, 1948, **561**, 70), but details of their isolation, etc., were not given. The 2-chloro-1-piperidinopropane used in the preparation described below was obtained from 1-piperidinopropan-2-ol (Wenker, *J. Amer. Chem. Soc.*, 1938, **60**, 158), which was characterised as its *picrate*, hexagonal prisms (from alcohol), m. p. 134—135° (Found : N, 15·0. $C_9H_{17}ON,C_6H_3O_7N_3$ requires N, 15·1%) (cf. the picrate, m. p. 114—115°, of 2-piperidinopropan-1-ol, prepared from ethyl α-piperidinopropionate by Adkins and Pavlic, *J. Amer. Chem. Soc.*, 1947, **69**, 3040).

2-Chloro-1-piperidinopropane (35 g.) was added dropwise during 1 hour to a well-stirred suspension of sodamide (8·5 g.) in diphenylmethyl cyanide (52 g.) and dry benzene (100 ml.) at 40—50°. After a further 30 minutes, the mixture was refluxed for 5 hours and then decomposed with water (100 ml.). The benzene layer (plus washings) was extracted with dilute sulphuric acid, and the basic material (58 g.) regenerated by addition of alkali to the washed acid extract.

The pure cyanides (Ia and IIa) were isolated from this basic material by making use of the fact that as bases the cyanide (IIa) tended to crystallise before the cyanide (Ia), whereas in the form of their halide salts the reverse was the case. For example :

Method (a). The basic mixture (24 g.) with light petroleum (b. p. 60—80°) (50 ml.) at 0° gave first crops which recrystallised from the same solvent to give pure *cyanide* (IIa) as hexagonal leaflets, m. p. 84—85° (Found : N, 8·8. $C_{20}H_{22}N_2$ requires N, 8·8%). The *hydrochloride* crystallised from alcohol–ether in needles, m. p. 200—201° (Found : N, 7·85; Cl, 10·0. $C_{20}H_{23}N_2,HCl$ requires N, 7·9; Cl, 10·0%), and the *hydrobromide* crystallised from the same solvent in leaflets, m. p. 170—172° (Found : N, 7·1; Br, 20·2. $C_{20}H_{23}N_2,HBr$ requires N, 7·0; Br, 20·1%). The *methiodide* crystallised from alcohol–ether in minute, slender, rectangular prisms, m. p. 169—171° (Found : N, 6·1; I, 27·6. $C_{20}H_{25}N_2I$ requires N, 6·1; I, 27·6%).

Later crops and the residues with hydrobromic acid formed a mixture of salts, which on fractional crystallisation from alcohol and a little ether gave the *hydrobromide* of the cyanide (Ia) as long needles, m. p. 239—241° (Found : N, 7·0; Br, 20·3. $C_{20}H_{23}N_2,HBr$ requires N, 7·0; Br, 20·1%). The free *base* separated from light petroleum (b. p. 60—80°) in minute needles, m. p. 105—106° (Found : N, 8·8. $C_{20}H_{22}N_2$ requires N, 8·8%), and the *hydrochloride* crystallised from alcohol–ether in well-defined rectangular prisms, m. p. 226—227° (Found : N, 7·95; Cl, 10·6. $C_{20}H_{23}N_2,HCl$ requires N, 7·9; Cl, 10·0%). The *methiodide* crystallised from alcohol in minute, pointed prisms, m. p. 228—229° (Found : N, 6·1; I, 27·5. $C_{20}H_{25}N_2I$ requires N, 6·1; I, 27·6%).

Method (b). The basic mixture (80 g.) from the sodamide reaction was distilled and the fraction (74 g.), b. p. 206—234°/5 mm., converted into a mixture of hydrobromides. Treatment of the anhydrous hydrobromides with acetone (230 ml.) gave the hydrobromide of cyanide (Ia) (32 g.) in pure form. The mother liquors yielded basic material, which on crystallisation gave the cyanide (IIa).

5-Piperidino-3 : 3-diphenyl-4-methylpentan-2-one (Ib).—The cyanide (Ia) (10 g.) in xylene (10 ml.) was added to the Grignard reagent from methyl iodide (13·6 g.), magnesium (2·3 g.), and dry ether (25 ml.). After 4 hours at 100° the xylene was removed under reduced pressure, and the reaction product decomposed with concentrated sodium hydroxide solution and taken to dryness. The residue was extracted with ether, which was then shaken with dilute hydrochloric acid. After removal of some unchanged cyanide hydrochloride, which separated, the acid solution was evaporated to dryness. The residue was taken up in methyl ethyl ketone, and (after removal of a small amount of ammonium chloride) precipitated with ether. The resulting deliquescent hydrochloride was converted through the oily base into the *pentanone nitrate*, which crystallised from water in tablets and from alcohol in needles, m. p. 195° (decomp.) (Found : N, 6·9. $C_{20}H_{24}ON,HNO_3$ requires N, 7·0%).

6-Piperidino-4 : 4-diphenyl-5-methylhexan-3-one (Id).—The cyanide (Ia) (32 g.) in xylene (30 ml.) was added to the Grignard reagent from magnesium (7·3 g.), ethyl bromide (32·7 g.), and ether (75 ml.), and the product extracted with ether, as described above. After purification of this extract through the acid solution, the resulting basic oil (26·5 g.) was dissolved in alcoholic hydrogen chloride, and the solution evaporated to dryness. The residue, refluxed with methyl ethyl ketone, yielded the insoluble *dihydrochloride* of the ketimine (Ic) (18·2 g.), which crystallised from alcohol in needles, m. p. 193° (decomp.), very soluble in water (Found : N, 6·6; Cl, 16·7. $C_{22}H_{29}N_2,2HCl$ requires N, 6·7; Cl, 16·8%).

The ketimine dihydrochloride, refluxed for 2·5 hours with 20% hydrobromic acid (75 ml.), gave an oily hydrobromide layer, which was purified by conversion through the base into the *ketone hydrochloride* (as Id); this formed needles, m. p. 197—198°, from methyl ethyl ketone (Found : N, 3·75; Cl, 9·15. $C_{22}H_{31}ON,HCl$ requires N, 3·6; Cl, 9·2%). The *hydrobromide* crystallised in needles, m. p. 208—209° (Found : N, 3·3; Br, 18·7. $C_{22}H_{31}ON,HBr$ requires N, 3·3; Br, 18·6%), and the *hydrogen sulphate* as micro-crystals, m. p. 219—221° (Found : N, 3·15; S, 7·2. $C_{22}H_{31}ON,H_2SO_4$ requires N, 3·1; S, 7·15%), both from alcohol–ether.

1-Piperidino-3 : 3-diphenyl-2-methylheptan-4-one (If).—The cyanide (Ia) (10 g.) in xylene (10 ml.) was added to *n*-propylmagnesium bromide (18·5 g.) in ether (25 ml.), and the mixture heated at 100° for 5 hours. The basic oil, extracted as described above, was converted into the hydrobromide, which, after being washed with hot methyl ethyl ketone and crystallised from alcohol–ether, gave the *ketimine dihydrobromide* (Ie) as granules, m. p. 215—216° (Found : N, 5·3; Br, 30·6. $C_{23}H_{33}N_2,2HBr$ requires N, 5·3; Br, 30·5%). The *dihydrochloride*, purified in the same way, melted at 192—194° (Found : N, 6·1; Cl, 16·2. $C_{23}H_{34}N_2,2HCl$ requires N, 6·4; Cl, 16·3%).

The dihydrobromide (Ie) (6 g.), refluxed for 2 hours with 20% hydrobromic acid (30 ml.), gave an oily lower layer, which, after being washed with water and recrystallised first from methyl ethyl ketone and then from alcohol–ether, gave the *ketone hydrobromide* (as If) as rectangular plates, m. p. 205—206° (Found : N, 3·25; Br, 17·7. $C_{23}H_{33}ON,HBr$ requires N, 3·15; Br, 18·0%).

5-Piperidino-3 : 3-*diphenylhexan*-2-*one* (IIb).—The basic oily product (14 g.) from the cyanide (IIa) (18 g.) in xylene (25 ml.) and methylmagnesium iodide (28·3 g.) in ether (45 ml.), prepared and isolated as described in previous examples, gave the *ketone hydrochloride* (as IIb) as crystalline granules (5·5 g.), m. p. 174—175°, from alcohol–ether (Found : N, 3·8; Cl, 9·6. $C_{23}H_{29}ON,HCl$ requires N, 3·8; Cl, 9·5%).

6-Piperidino-4 : 4-*diphenylheptan*-3-*one* (IIc).—The basic reaction product from (IIa) (10·6 g.) in xylene (50 ml.) and ethylmagnesium bromide (13·5 g.) in ether (50 ml.) was extracted with hydrochloric acid. On cooling, crude *ketone hydrochloride* (as IIc) separated and was purified by crystallisation first from water (plus a little hydrochloric acid) and then from wet alcohol–ether. It formed minute prisms, m. p. 123—126° (Found : N, 3·45; Cl, 9·3. $C_{24}H_{31}ON,HCl$ requires N, 3·6; Cl, 9·2%) (Bockmühl and Ehrhart, *loc. cit.*, have recorded m. p. 189° for this hydrochloride). The *hydrobromide*, m. p. 103—106°, crystallised from water (Found : N, 3·4; Br, 18·5. $C_{24}H_{31}ON,HBr$ requires N, 3·3; Br, 18·8%), and the *picrate* from alcohol in rectangular prisms, m. p. 137—138° (Found : N, 9·65. $C_{30}H_{34}ON_4C_6H_3O_7N_3$ requires N, 9·7%).

7-*Piperidino*-5 : 5-*diphenyloctan*-4-*one* (IId).—The product (9·5 g.), from the cyanide (IIa) (10 g.) and *n*-propylmagnesium iodide (18·5 g.), gave a deliquescent hydrochloride, but its *nitrate* was sparingly soluble in water and crystallised from alcohol in pyramidal tablets, m. p. 167° (decomp.) (Found : N, 6·5. $C_{25}H_{34}ON,HNO_3$ requires N, 6·6%).

γ-*Piperidino*-α-*diphenylvaleramide* (IIe).—The cyanide (IIa) (4 g.) was heated with 66% v/v sulphuric acid at 180° for 5 minutes. The mixture, which had darkened considerably, was then diluted with water and made alkaline. The semi-solid *amide* that separated crystallised from dilute alcohol in tablets, m. p. 156—157° (Found : N, 8·4. $C_{23}H_{24}ON_2$ requires N, 8·3%).

3-*Piperidino*-1 : 1-*diphenylbutane* (IIf).—*Method* (a). A well-stirred suspension of sodamide (5 g.) in a solution of the cyanide (IIa) (5 g.) in toluene (20 ml.) was refluxed for 6 hours and then decomposed with dilute hydrochloric acid. The ether-washed aqueous layer was made alkaline and extracted with ether. The ethereal residue with light petroleum afforded some unchanged cyanide (IIa) (3 g.), m. p. 83°, but the oil from the mother-liquors gave the butane hydrochloride (as IIf) as rectangular plates, m. p. 211—212°, from alcohol–ether (Found : N, 4·3; Cl, 10·7. Calc. for $C_{21}H_{27}N,HCl$: N, 4·25; Cl, 10·7%) (Bockmühl and Ehrhart, *loc. cit.*, give m. p. 214—215°). *Method* (b). The propionyl (IIe) hydrochloride (1·6 g.), ethylene glycol (10 ml.), and finely-divided potassium hydroxide (2 g.) were refluxed together for 17 hours. The basic product, extracted with ether, was dissolved in hydrochloric acid, and from this the butane hydrochloride (as IIf) (0·5 g.) was readily isolated by reason of its low solubility in hot methyl ethyl ketone.

Determination of the Structure of the Cyanide (Ia) *by Exhaustive Methylation.*—The methiodide of the cyanide (Ia) (42 g.), dissolved in water (3 l.) at 90—95°, was treated with moist silver oxide freshly prepared from silver nitrate (46·5 g.). After being stirred vigorously for 30 minutes at this temperature, the suspension was filtered and the filtrate concentrated *in vacuo* to a syrup (*A*). The distillate, absorbed in dilute hydrochloric acid and made alkaline, gave an ethereal extract which, on distillation, afforded 1-methylpiperidine (4·2 g.), b. p. 105—107°; picrate, m. p. 222° (Found : C, 43·9; H, 4·9; N, 17·0. Calc. for $C_6H_{13}N,C_6H_3O_7N_3$: C, 43·9; H, 4·9; N, 17·1%). The undistilled syrup (*A*) was shaken with water and ether. The ethereal extract on distillation gave 1 : 1-diphenyl-2-methylallyl cyanide (III) (12·5 g.), b. p. 162—165°/4 mm., m. p. 64—65° (Found : C, 87·4; H, 6·3; N, 6·2. Calc. for $C_{17}H_{15}N$: C, 87·5; H, 6·4; N, 6·0%) [cf. Schultz, Robb, and Sprague, *loc. cit.*], and a residual solid, which on being washed with ether and crystallised from aqueous alcohol gave 1 : 1-*diphenyl*-2-*methylallylformamide* (IV) as slender needles, m. p. 180—181° (Found : C, 81·2; H, 6·85; N, 5·5. $C_{18}H_{17}ON$ requires C, 81·2; H, 6·8; N, 5·6%).

Hydrogenation of (III) (11·8 g.), as described by Schultz, Robb, and Sprague (*loc. cit.*), gave 2 : 2-diphenyl-3-methyl-*n*-butylamine (V) (10·3 g.), b. p. 125—136°/0·1 mm. (Found : N, 5·5. Calc. for $C_{17}H_{21}N$: N, 5·85%). Its *phenylureido*-derivative (needles, m. p. 204—205°, from alcohol) (Found : C, 80·3; H, 7·2; N, 7·8. $C_{24}H_{26}ON_2$ requires C, 80·5; H, 7·3; N, 7·8%) gave no m. p. depression on admixture with the same derivative of the butylamine synthesised from diphenylmethyl cyanide and *iso*propyl iodide (Schultz *et al.*, *loc. cit.*). For purposes of comparison the isomeric 2 : 2-diphenyl-*n*-amylamine was synthesised from diphenylmethyl cyanide and *n*-propyl iodide (Schultz *et al.*, *loc. cit.*) and its *phenylureido*-derivative prepared (needles, m. p. 194°, from alcohol) (Found : C, 80·6; H, 7·8; N, 7·8. $C_{24}H_{26}ON_2$ requires C, 80·5; H, 7·3; N, 7·8%).

Confirmation of the Structure of the Cyanide (IIa) *by an Alternative Synthesis.*—3-Bromo-1 : 1-diphenyl-*n*-butyl cyanide (X) (20 g.) (prepared by the method of Easton *et al.*, *J. Amer. Chem. Soc.*, 1947, **69**, 2941), was refluxed with piperidine (14·5 g.) for 12 hours, and, after cooling, excess of 40% sodium hydroxide was added. The mixture was extracted with ether, and the ethereal solution shaken with dilute acid. Fractionation of the base, liberated from the acid extract, yielded the cyanide (IIa) as a viscous oil, b. p. 224—228°/2·5 mm., which crystallised from light petroleum in hexagonal leaflets, m. p. 81—82°, identical with the product already described.

1-*Chloro*-3-*piperidinopropane*.—3-Piperidinopropan-1-ol (174 g.) (prepared in 94% yield from piperidine, allyl alcohol, and sodium, as described by Hromatka, *loc. cit.*) in benzene (175 ml.) was added to a stirred solution of thionyl chloride (145 g.) in the same solvent (145 ml.) at 0°. After 2 hours' refluxing, the resulting solid hydrochloride (231 g.) was collected and washed with benzene and ether. It crystallised from alcohol–ether in slender rectangular plates, m. p. 213—214° (Found : N, 6·9; Cl, 35·8. Calc. for $C_8H_{16}NCl,HCl$: N, 7·1; Cl, 35·8%).

4-*Piperidino*-1 : 1-*diphenyl*-n-*butyl Cyanide* (XIa).—1-Chloro-3-piperidinopropane [from the hydrochloride (34 g.)] reacted with diphenylmethyl cyanide (42 g.) in dry benzene (85 ml.) in the presence of sodamide (6·8 g.), and the basic product (38 g.) was isolated as described for the cyanides (Ia) and (IIa). Distillation yielded an oily base (35 g., 64%), b. p. 223—228°/3·5 mm., which gave a *hydrochloride* crystallising from methyl ethyl ketone in octahedral plates, m. p. 187—188° (Found : N, 8·0; Cl, 10·0. $C_{22}H_{28}N_2,HCl$ requires N, 7·9; Cl, 10·0%). The *hydrogen sulphate* crystallised from alcohol in long

slender prisms, m. p. 160—161°, almost insoluble in methyl ethyl ketone (Found: N, 6·75; S, 7·7. $C_{22}H_{31}N_3,H_2SO_4$ requires N, 6·7; S, 7·7%).

6-*Piperidino*-3:3-*diphenylhexan*-2-*one* (XIb).—The product from the reaction of (XIa) (16·5 g.) in xylene with methylmagnesium iodide (25·8 g.) in ether was isolated. This oily ketone (XIb), b. p. 220—224°/2·5 mm., gave a ***hydrogen sulphate*** crystallising from alcohol in slender prisms, m. p. 172—173° (Found: N, 3·3; S, 7·4. $C_{25}H_{33}ON,H_2SO_4$ requires N, 3·2; S, 7·4%), and a ***hydrobromide*** as rectangular plates, m. p. 209—210°, from the same solvent (Found: N, 3·4; Br, 19·3. $C_{25}H_{33}ON,HBr$ requires N, 3·4; Br, 19·2%).

7-*Piperidino*-4:4-*diphenylheptan*-3-*one* (XIc).—Distillation of the basic oil from interaction of (XIa) (12·5 g.) and ethylmagnesium bromide (15·9 g.) in xylene gave the ***ketone*** (XIc), b. p. 228—232°/2·5 mm. (Found: N, 4·0. $C_{24}H_{31}ON$ requires N, 4·0%), which afforded a ***hydrobromide*** as rectangular prisms, m. p. 150—151°, from methyl ethyl ketone–ether (Found: N, 3·3; Br, 18·7. $C_{24}H_{31}ON,HBr$ requires N, 3·25; Br, 18·6%), and a microcrystalline ***hydrogen sulphate***, m. p. 192—193°, from ethyl alcohol (Found: N, 3·5; S, 7·1. $C_{24}H_{31}ON,H_2SO_4$ requires N, 3·1; S, 7·15%).

8-*Piperidino*-5:5-*diphenyloctan*-4-*one* (XId).—This was prepared from (XIa) (14·6 g.) and n-propylmagnesium iodide (3 mols.). It boiled at 231—233°/2 mm., and was purified by conversion into the ***hydrogen sulphate***; micro-crystals, m. p. 193—194°, from alcohol (Found: N, 3·35; S, 7·0. $C_{26}H_{35}ON,H_2SO_4$ requires N, 3·0; S, 6·9%). Its ***hydrobromide*** formed parallelogrammatic plates, m. p. 154—155°, from methyl ethyl ketone–ether (Found: N, 3·2; Br, 18·3. $C_{26}H_{35}ON,HBr$ requires N, 3·15; Br, 18·0%).

Preparation of Compounds of the Type (XII).—3-Diethylamino-1:1-diphenylpropyl cyanide (XIIa) was prepared in a manner similar to that subsequently described by Dupré *et al.* (*loc. cit.*). It formed a ***hydrobromide***, crystallising from alcohol–ether in rectangular leaflets, m. p. 131—132° (Found: N, 7·4; Br, 21·4. $C_{20}H_{24}N_2,HBr$ requires N, 7·5; Br, 21·4%), and a ***methiodide***, crystallising from alcohol in long needles, m. p. 185—190° (Found: N, 6·8; I, 28·9. $C_{21}H_{27}N_2I$ requires N, 6·4; I, 29·3%).

With ethylmagnesium bromide (XIIa) afforded the ketone (XIIb) (cf. Dupré *et al.*, *loc. cit.*), the ***hydrobromide*** of which crystallised from alcohol–ether in prisms, m. p. 116—119° (Found: N, 3·4. $C_{22}H_{29}ON,HBr$ requires N, 3·3%).

A solution of (XIIa) (2 g.) in 50% sulphuric acid (5 ml.), refluxed for 1 hour, diluted, made alkaline, and cooled, gave ***γ-diethylamino-αα-diphenylbutyramide*** (XIIc) as a crystalline precipitate, m. p. 80—86° (Found: N, 8·8. $C_{20}H_{26}ON_2$ requires N, 9·0%). The neutralised filtrate, on concentration *in vacuo*, gave the corresponding carboxylic acid (XIId) as a white precipitate, m. p. 183—184° (decomp.) (Found: N, 4·6. Calc. for $C_{20}H_{25}O_2N$: N, 4·6%).

Treatment of (XIId) with excess of diazomethane in ether for 3 days at room temperature gave a solution of the ethyl ester (XIIe), the ***methiodide*** of which crystallised from alcohol–ether in clusters of needles, m. p. 133—135° (Found: OEt, 9·4; I, 26·3. $C_{23}H_{31}O_2NI$ requires OEt, 9·4; I, 26·4%). The same acid, heated at 200° for 20 minutes, made alkaline and extracted with ether, afforded 3-diethylamino-1:1-diphenylpropane (XIIf) (Eisleb, *Ber.*, 1941, **74**, 1438), which formed a ***hydrobromide***, crystallising in needles, m. p. 131—132° (Found: N, 4·0; Br, 23·3. $C_{19}H_{25}N,HBr$ requires N, 4·0; Br, 23·0%), and a methiodide crystallising in prisms, m. p. 158—159° (Adamson, *loc. cit.*) (Found: N, 3·6; I, 30·9. Calc. for $C_{20}H_{28}NI$: N, 3·4; I, 31·1%), both from alcohol–ether.

3-*Diethylamino*-1:1-*diphenyl*-2-*methyl*-n-*propyl Cyanide* (XIIIa) and **3-*Diethylamino*-1:1-*diphenyl*-n-*butyl Cyanide*** (XIVa).—A well-stirred solution of 2-chloro-1-diethylaminopropane (48 g.) (from its hydrochloride; Kerwin *et al.*, *J. Amer. Chem. Soc.*, 1947, **69**, 2964) and diphenylmethyl cyanide (65 g.) in dry benzene (200 ml.) at 70—80° was treated with sodamide (13 g.) in small portions and the reaction completed by heating and stirring the solution for 1 hour more. The mixture was then decomposed with water, the benzene removed *in vacuo*, and the residual oily mixture extracted with ether. The ethereal extract was shaken with dilute hydrochloric acid, and the acid extract taken to dryness. Fractional crystallisation of the residue from alcohol eventually gave the less-soluble cyanide (XIIIa) ***hydrochloride*** as tablets, m. p. 234—238° (Found: N, 8·3; Cl, 10·7. $C_{21}H_{26}N_2,HCl$ requires N, 8·2; Cl, 10·4%), and the more-soluble cyanide (XIVa) ***hydrochloride*** as rectangular prisms, m. p. 165—167° (Found: N, 8·3; Cl, 10·6. $C_{21}H_{26}N_2,HCl$ requires N, 8·2; Cl, 10·4%). The ***hydrobromide*** of (XIIIa) [tablets, m. p. 241—242° (Found: N, 7·5; Br, 21·1. $C_{21}H_{26}N_2,HBr$ requires N, 7·2; Br, 20·7%)] was likewise less soluble in both alcohol and water than the ***hydrobromide*** of (XIVa) [rectangular plates, m. p. 189—190° (Found: N, 7·5; Br, 21·2. $C_{21}H_{26}N_2,HBr$ requires N, 7·2; Br, 20·7%)], but this difference could not be used in their separation as they appeared to form a eutectic mixture (1 : 1), which melted steadily at 185—190°, despite several recrystallisations.

The ***base*** (XIIIa) crystallised slowly from its evaporating solution in light petroleum (b. p. 60—80°) in rectangular plates, m. p. 43—46° (Found: N, 9·2. $C_{21}H_{26}N_2$ requires N, 9·15%), but the base (XIVa) could not be induced to crystallise.

The ***methiodide*** of (XIIIa) crystallised from alcohol in slender prisms, m. p. 228° (decomp.), sparingly soluble in water (Found: N, 5·5; I, 26·0. $C_{22}H_{29}N_2I$ requires N, 6·25; I, 28·3%). The ***methiodide*** of (XIVa) crystallised from alcohol–ether in needles, m. p. 177—179° (Found: N, 5·8; I, 25·5. $C_{22}H_{29}N_2I$ requires N, 6·25; I, 28·3%), but separated from water as an oil.

Determination of the Structure of (XIIIa) ***and of*** (XIVa).—A solution of the methiodide of (XIIIa) (7 g.) in hot water (250 ml.) was poured into silver oxide (from 7·5 g. of silver nitrate) suspended in water (50 ml.). After being boiled gently for 1 hour and filtered, the liquid was evaporated *in vacuo*, and the oil that separated was extracted with ether. On removal of the solvent, this oil solidified and was crystallised from light petroleum (b. p. 40—60°) to give 1 : 1-diphenyl-2-methylallyl cyanide (III), m. p. 62—63°, identical with that obtained as already described. The methiodide of (XIVa), similarly treated with

silver oxide, afforded a product which on being washed with light petroleum (b. p. 60—80°) gave a solid crystallising from benzene–light petroleum in square tablets, m. p. 156—158° (Found: N, 5·6. Calc. for $C_{17}H_{17}ON$: N, 5·6%). This very probably consisted of αα-diphenyl-β-vinylpropionamide (XV), as it differed from (IV) but was apparently identical with the amide obtained from 3-dimethylamino-1 : 1-diphenyl-α-butyl cyanide by Schultz *et al.* (*loc. cit.*). The ether-extracted mother-liquors on acidification gave the lactone (IX), m. p. 111—112° (Found: C, 81·0; H, 6·4. Calc. for $C_{17}H_{16}O_2$: C, 81·2; H, 6·3%), identical with that obtained by hydrolysis of 1 : 1-diphenylbut-3-enyl cyanide (VII) (Easton *et al.*, *loc. cit.*).

6-*Diethylamino*-4 : 4-*diphenyl*-5-*methylhexan*-3-*one* (XIIIc).—A portion of the basic oil (11 g.) from the interaction of (XIIIa) (12 g.) and ethylmagnesium bromide (11·8 g.) in xylene on distillation gave a fraction, b. p. 148—150°/0·05 mm., probably (analysis) the intermediate *ketimine* (XIIIb) (Found: N, 8·3. $C_{23}H_{29}N_1$ requires N, 8·3%), which afforded a *dihydrochloride*, crystallising from alcohol–ether in leaflets, m. p. 179—180° (Found: N, 6·4; Cl, 17·0. $C_{23}H_{29}N_1,2HCl$ requires N, 6·6; Cl, 17·3%). The bulk of the basic oil was therefore refluxed with 20% hydrobromic acid for 3 hours and the product diluted with water. After 2 days at 0°, the solid that had separated was crystallised from alcohol–ether to give the ketone (XIIIc) *hydrobromide* as prisms, m. p. 189—191° (Found: N, 3·2; Br, 19·3. $C_{23}H_{31}ON,HBr$ requires N, 3·35; Br, 19·1%). The corresponding *hydrochloride*, m. p. 166—169° (Found: N, 3·7; Cl, 9·7. $C_{23}H_{31}ON,HCl$ requires N, 3·75; Cl, 9·5%), showed a depression in m. p. on admixture with the above ketimine dihydrochloride.

6-*Diethylamino*-4 : 4-*diphenylheptan*-3-*one* (XIVb).—The basic oil from the interaction of (XIVa) (17 g.) and ethylmagnesium bromide (17 g.) was dissolved in hydrochloric acid, and the solution evaporated to dryness. The residue when treated with acetone gave some ammonium chloride, which was removed, and a filtrate, which on evaporation and reconversion into the base afforded the ketone (XIVb) *hydrobromide* as well-defined needles, m. p. 135—138° (shrinking at 115—120°), from alcohol–ether (Found: N, 3·2. $C_{23}H_{31}ON,HBr$ requires N, 3·35%).

*N-Benzyl-N-methyl-2-aminoethyl Chloride.**—*N*-Benzyl-*N*-methyl-2-aminoethanol (33 g.), b. p. 133—136°/14 mm., was prepared by interaction of benzylmethylamine (56 g.) and ethylene oxide (28 ml.) under pressure at 65° for 3 hours and fractionation of the product (Mannich and Kuphal used benzylmethylamine and ethylene chlorohydrin, *Arch. Pharm.*, 1912, **250**, 542). With thionyl chloride (19·5 ml.) in chloroform (50 ml.) this gave *N-benzyl-N-methyl-2-aminoethyl chloride hydrochloride* (30 g.), which crystallised readily from alcohol–ether in needles, m. p. 140—141° (Found: N, 6·6; Cl, 32·3. $C_{10}H_{14}NCl,HCl$ requires N, 6·4; Cl, 32·3%).

3-(*Benzylmethylamino*)-1 : 1-*diphenylpropyl Cyanide*.—Dupré *et al.* (*loc. cit.*) have recently prepared this compound and the corresponding ketone by way of 3-bromo-1 : 1-diphenylpropyl cyanide.

Diphenylmethyl cyanide (8 g.), *N*-benzyl-*N*-methyl-2-aminoethyl chloride (9 g.), and sodamide (2 g.) reacted in dry benzene as described for the preparation of the cyanides (XIIIa) and (XIVa). The product was decomposed with water, evaporated to remove benzene, and extracted with ether. The ethereal extract, with hydrochloric acid, was converted into a sparingly-soluble oily hydrochloride which, after being washed with ether, was dissolved in chloroform. As the hydrochloride failed to crystallise it was converted into the base and distilled; the fraction, b. p. 220—230°/0·4 mm., gave a *methiodide* which crystallised from alcohol in rectangular prisms, m. p. 204—206° (Found: N, 5·8; I, 26·9. $C_{25}H_{27}N_1I$ requires N, 5·8; I, 26·4%).

6-(*Benzylmethylamino*)-4 : 4-*diphenylhexan*-3-*one*.—This was prepared from the corresponding cyanide and ethylmagnesium bromide and gave an oily, sparingly-soluble hydrochloride,† and a crystalline *methiodide* [needles, m. p. 189—190°, from alcohol–ether (Found: I, 25·1. $C_{27}H_{32}ONI$ requires I, 24·8%)], which showed a depression in m. p. on admixture with the corresponding cyanide methiodide.

2-*Dicyclohexylaminoethyl Chloride*.—2-*Dicyclo*hexylaminoethanol (55 g.), b. p. 178—182°/14 mm., was prepared in improved yield (73%) by the interaction of ethylene oxide (15 ml.) and dicyclohexylamine (60 ml.) under pressure at 100° for 2 hours, then at 150° for two more hours, and finally at 200° for 6 hours, followed by fractionation of the product (Blicke and Maxwell, *J. Amer. Chem. Soc.*, 1942, **64**, 429, obtained a 55% yield from dicyclohexylamine and ethylene chlorohydrin). Dicyclohexylaminoethyl chloride hydrochloride, from the alcohol and thionyl chloride (B.P. 351,605), crystallised from alcohol–ether in minute cubes, m. p. 184° (Found: N, 5·0; Cl, 25·8. Calc. for $C_{14}H_{28}NCl,HCl$: N, 5·0; Cl, 25·4%).

3-*Dicyclohexylamino*-1 : 1-*diphenylpropyl Cyanide*.—The product from the interaction in benzene of diphenylmethyl cyanide (8 g.), dicyclohexylaminoethyl chloride (12 g.), and sodamide (1·9 g.) [obtained as described under 3-benzylmethylamino-1 : 1-diphenylpropyl cyanide] was extracted with ether, and the extract washed with dilute hydrochloric acid. The residue obtained by evaporation of the acid washings was crystallised from alcohol–ether and gave the *cyanide hydrochloride* as hexagonal tablets, m. p. 196—198°, sparingly soluble in water (Found: N, 6·3; Cl, 8·0. $C_{28}H_{34}N_2,HCl$ requires N, 6·4; Cl, 8·15%). The cyanide base, m. p. 71—75°, with methyl iodide under pressure at 100° gave a *methiodide*, m. p. 104—110°, from alcohol–ether (Found: N, 5·3; I, 23·4. $C_{29}H_{37}N_2I$ requires N, 5·2; I, 23·4%).

6-*Dicyclohexylamino*-4 : 4-*diphenylhexan*-3-*one*.—The product from the interaction of the preceding cyanide and ethylmagnesium bromide gave an amorphous *ketone hydrochloride* (Found: N, 3·3; Cl, 7·6. $C_{28}H_{41}ON,HCl$ requires N, 3·0; Cl, 7·6%) and a crystalline methiodide, m. p. 187—192°.

4-*Dimethylamino*-2 : 2-*diphenylamylamine* (XVI; R = H).—3-Dimethylamino-1 : 1-diphenylbutyl cyanide (Part III, *loc. cit.*) (10 g.), liquid ammonia (20 ml.), and Raney nickel (3 g.) in methyl alcohol

* Bergel *et al.* (*J.*, 1944, 269) have used this base without describing it.

† Bockmühl and Ehrhart (*loc. cit.*) give m. p. 142—143° for this hydrochloride but do not describe its preparation.

(50 ml.) were treated with hydrogen at 170° (5 atmospheres) for 6 hours. The filtered product on distillation gave an oil, b. p. 214—218°/15 mm., which later solidified. Crystallisation from light petroleum (b. p. 60—80°) gave (XVI; R = H) as prisms, m. p. 67—70° (Found: N, 9·7. $C_{19}H_{26}N_2$ requires N, 9·5%). Its *acetyl* derivative (XVI; R = COMe) crystallised from light petroleum (b. p. 80—90°) in rectangular tablets, m. p. 119—121° (Found: N, 8·6. $C_{21}H_{28}ON_2$ requires N, 8·6%), and gave a *hydrobromide* as needles, m. p. 227—229°, from alcohol–ether (Found: N, 6·8; Br, 19·7. $C_{21}H_{29}ON_2HBr$ requires N, 6·9; Br, 19·7%). The *phenylureido*-derivative (XVI; R = CO·NHPh) crystallised from benzene–light petroleum in rectangular granules, m. p. 170—173° (Found: N, 10·6. $C_{26}H_{31}ON_3$ requires N, 10·5%), which gave a somewhat gelatinous *hydrochloride*, m. p. 234—238°, from water (Found: N, 9·7. $C_{26}H_{31}ON_3HCl$ requires N, 9·6%).

4-*Dimethylamino*-2 : 2-*diphenyl*-3-*methylbutylamine* (XVII; R = H).—This *amine*, b. p. 218—220°/15 mm., was prepared by hydrogenation of 3-dimethylamino-1 : 1-diphenyl-2-methylpropyl cyanide (Part III, *loc. cit.*) as described above for the amylamine (XVI; R = H); it gave a *dihydrobromide* as minute granules, m. p. 231—232°, from alcohol–ether (Found for the base: N, 10·3. $C_{19}H_{26}N_2$ requires N, 9·5%. Found for the dihydrobromide: N, 6·5; Br, 35·9. $C_{19}H_{26}N_2,2HBr$ requires N, 6·3; Br, 36·0%). Its *acetyl* derivative (XVII; R = COMe) crystallised from light petroleum (b. p. 60—80°) in small needles, m. p. 104—106° (Found: N, 8·6. $C_{21}H_{28}ON_2$ requires N, 8·6%), and formed a *hydrobromide* crystallising from alcohol–ether in granules, m. p. 219—221° (Found: N, 6·6; Br, 19·8. $C_{21}H_{29}ON_2HBr$ requires N, 6·9; Br, 19·7%).

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445. *The Apparent Induction of Polarity in Non-polar Solutes by Polar Solvents.*

By H. G. Holland and R. J. W. Le Fèvre.

Earlier observations of the phenomena covered by the title have been repeated and extended, and a more certain extrapolation procedure applied. Solutes such as carbon disulphide, benzene, *cyclo*hexane, diphenyl, etc., dissolved in nitrobenzene appear to develop moments ranging from 1·2 to 2 D. The effects are not smoothly proportional to the corresponding molecular refractions, but use of the latter in conjunction with dimensions read off scale drawings has afforded an empirical equation, $\mu^2_{\text{induced}} = \mu^2_2 . R_1 \text{Exp.}(-k^2)/A_2B_2C_2$, by which the experimental results in chloro- as well as nitro-benzene may be satisfactorily forecast.

Le Fèvre and Le Fèvre (*J.*, 1936, 487), from measurements of the dielectric constants and densities of dilute solutions of benzene, carbon disulphide, and other centro-symmetric molecules in chlorobenzene, nitrobenzene, benzonitrile, etc., reported signs that in such media the solutes, ordinarily non-polar, acquired apparent polarisations of considerable magnitude.

The actual numerical results were, however, computed by the conventional mixture formula, $P_{12} = P_1f_1 + P_2f_2$, where f and P represent molar fractions and molecular polarisation, and subscripts 1, 2, and 12, refer to solute, solvent, and solution, respectively. The Le Fèvre's commented at some length on the difficulty, inseparable from the application of this procedure to the systems indicated above, of estimating the contributions made by P_2 to the total polarisations of the solutions. It was clear that P_2 should not be taken as invariant with concentration, but rather as increasing in some manner with f_1. Nevertheless, an attempt to deduce " corrections " from the data of Pal (*Phil. Mag.*, 1930, **10**, 265) and Sutton and Jenkins (*J.*, 1935, 609) for benzene–nitrobenzene mixtures failed to eliminate the appearance of solute polarity in this one case, and strengthened the impression that the phenomenon was general.

During the intervening years several authors have adopted mathematical methods for extrapolating P_1 of a solute (in a non-polar solvent) to " infinite dilution " (cf. Le Fèvre, *Trans. Faraday Soc.*, 1950, **46**, 1, for refs.). In particular, equations showing ε_{12} and d_{12} as rectilinear with concentration of component 1 (cf. Hedestrand, *Z. physikal. Chem.*, 1929, *B*, **2**, 428; Le Fèvre and Vine, *J.*, 1937, 1805) are now known often to overaimplify—and thus misrepresent—relationships which really require extra terms involving the concentrations to powers higher than unity. In most instances when a wide composition range has not been covered, the introduction of f_1^3 (or w_1^3, *i.e.* the square of the weight fraction) provides adequate compensation (cf. Le Fèvre, *loc. cit.*), and $(w_2)_{w_1}$ or $(\delta d_2)_{w_1}$ [calculated as $(\varepsilon_{12} - \varepsilon_2)/w_1$ or $(d_{12} - d_2)/w_1$,

respectively] are found to have a straight-line dependence upon concentration. Their values at f_1 or $w_1 = 0$ can thus be obtained, and, when combined with directly determined constants for the pure solvent, yield the desired polarisation at infinite dilution. By following such a routine any inconstancy of P_2 need not mar the final figure for ${}_\infty P_1$.

The present work was intended to check the earlier findings of Le Fèvre and Le Fèvre by the method just outlined. Accordingly, we now report on solutions in nitrobenzene of benzene, *cyclo*hexane, naphthalene, decalin, diphenyl, and *p*-dichlorobenzene, using more solutions and a fuller choice of solutes than were taken in 1936. In each case equations to the curves between $(\alpha\varepsilon_2)_{w_1}$ or $(\beta d_2)_{w_1}$ and w_1 have been calculated from experimentally observed quantities, ${}_\infty P_1$ following therefore as $M_1[\rho_2(1 - \beta) + C\alpha\varepsilon_2]$, where α and β are the appropriate limiting coefficients and ρ_2 and C are as defined by Le Fèvre (*loc. cit.*). Our results are assembled in Table I together with, for comparison, the apparent moments * recorded by Le Fèvre and Le Fèvre.

TABLE I.

Apparent polarities of non-polar solutes in nitrobenzene.

Solute.	$(\alpha\varepsilon_2)_{w_1 = 0}$.	$(\beta d_2)_{w_1 = 0}$.	${}_\infty P_1$ (c.c.).	$[R_L]_D$ (c.c.).	μ, D.	μ, D.
Benzene	−67·2	−0·473	73·2	26·2	1·53	1·51 *
p-Dichlorobenzene	−42·7	+0·071	93·6	36·7	1·68	1·65 *
*cyclo*Hexane	−64·4	−0·692	91·1	27·7	1·75	—
Naphthalene	−51·3	−0·229	104·1	44·4	1·72	—
Decalin	−53·7	−0·467	132·6	44·1	2·10	—
Diphenyl	−51·7	−0·215	123·7	52·4	1·88	1·88 *

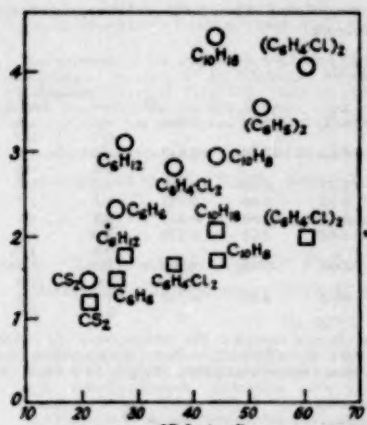
* See *J.*, 1936, 457.

In the three common cases the new determinations, made at 30°, confirm the older ones taken at 25°. For discussion, therefore, we will add the apparent moments previously observed in nitrobenzene of carbon disulphide (1·20 D.) and *pp'*-dichlorodiphenyl (2·00 D.).

DISCUSSION.

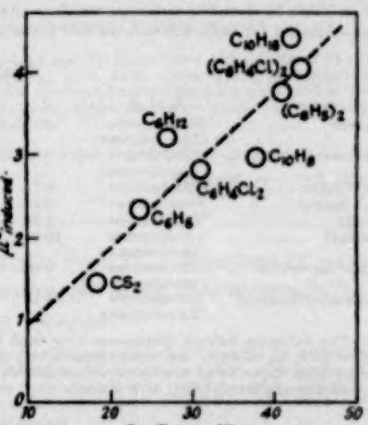
Le Fèvre and Le Fèvre (*loc. cit.*) noted that there was a rough proportionality between the induced moments and those of the solvent molecules. With the extended data now available,

FIG. 1.



Plot of $\mu_{induced}$ (□) and $\mu^2_{induced}$ (○) against the molecular refractivity.

FIG. 2.



however, it becomes obvious that such a relationship is not exact. Fig. 1 shows $\mu_{induced}$ or $\mu^2_{induced}$ plotted against the molecular-refractivity values for the solutes; since $[R_L]_D =$

$4\pi N\alpha/3$, where α c.c. is the average polarisability, the non-rectilinearity of both curves indicates an absence of a direct dependence of $\mu_{induced}$ on α.

Intuitively it seemed that the anisotropy of polarisability of the dissolved molecules needed to be introduced. Of a number of attempts, the following has shown greatest promise: scale drawings of the structures concerned have been constructed with Stuart's "Wirkungsradien" (*Z. physikal. Chem.*, 1935, *B*, **27**, 350; cf. Barclay and Le Fèvre, *J.*, 1950, 556) superimposed, and lengths, *A*, *B*, or *C*, read off in three perpendicular directions set so that *A* is the greatest, and of *B* and *C* the second is the lesser. (In what follows, dimensions of solutes or solvents are denoted by suffixes 1 or 2.) A constant, h^2, could then be computed for each species *via* $h^2 = [(A - B)^2 + (B - C)^2 + (C - A)^2]/(A + B + C)^2$ and an indication of the departure from spherical symmetry provided by Exp. $(-h^2)$, which is of course unity when $A = B = C$.

Fig. 2 shows the connection between $\mu^2_{induced}$ and $R_1 . \mathrm{Exp.}(-h^2)$.

Empirical Formulæ for the Induced Moments.—By accepting the implications of Fig. 2, an equation (among others) such as $\mu^2_{induced} = (R_1/K)\mathrm{Exp.}(-h^2)$ might apply. K would be a constant for the solvent, and indeed, by adopting a value of K about 11 for nitrobenzene, a set of "calculated" values follow in reasonable agreement with experiment:

Solvent: nitrobenzene.

Solute:	CS_2.	C_6H_6.	$C_6H_5Cl_2$.	C_6H_{12}.	$C_{10}H_8$.	$C_{10}H_{18}$.	$(C_6H_5)_2$.	$(C_6H_4Cl)_2$.
$\mu_{ind.}$ (calc.)	1·3	1·5	1·7	1·6	1·7	2·0	1·9	2·0
$\mu_{ind.}$ (found)	1·2	1·5	1·7	1·8	1·7	2·1	1·9	2·0

For the five of these substances examined in chlorobenzene by Le Fèvre and Le Fèvre a K value of *ca.* 55 may be used, though less satisfactorily, possibly because the moments found were in all cases *less* than 1 D., so that squaring magnifies the effects of experimental errors:

Solvent: chlorobenzene.

Solute:	CS_2.	C_6H_6.	$C_6H_5Cl_2$.	$(C_6H_5)_2$.	$(C_6H_4Cl)_2$.
$\mu_{ind.}$ (calc.)	0·6	0·7	0·8	0·9	0·9
$\mu_{ind.}$ (found)	0·5	0·7	0·8	1·0	0·8

The two constants involved above ($K = 11$ or 55) correspond nearly to the reciprocal of $\mu^2_{gas}/A_2B_2C_2$. Accordingly we propose as a general equation:

$$\mu^2_{induced} = \mu_2{}^2_{gas} . R_1 . \mathrm{Exp}(-h^2)/A_2B_2C_2,$$

and in Table II (last two columns) we show the concordance between calculation and measurement obtained for both solvents on this common basis.

TABLE II.

Solute.	Solvent.	A_1.	B_1.	C_1.	Exp.$(-h^2)$.	$(\mu_{induced})$, calc.	found.
Benzene	Nitrobenzene	6·70	6·05	2·90	0·904	1·4	1·5
"	Chlorobenzene	"	"	"	"	0·7	0·7
p-Dichlorobenzene	Nitrobenzene	9·46	6·05	3·16	0·843	1·6	1·7
"	Chlorobenzene	"	"	"	"	0·8	0·8
*cyclo*Hexane	Nitrobenzene	6·71	5·42	4·50	0·974	1·5	1·8
Naphthalene	Nitrobenzene	8·98	7·18	2·90	0·851	1·8	1·7
Decalin	Nitrobenzene	7·94	6·71	4·50	0·951	1·9	2·1
Diphenyl	Nitrobenzene	10·96	6·05	2·90	0·779	1·8	1·9
"	Chlorobenzene	"	"	"	"	0·9	1·0
Carbon disulphide	Nitrobenzene	6·40	3·08	3·08	0·869	1·2	1·2
"	Chlorobenzene	"	"	"	"	0·6	0·5
pp'-Dichlorodiphenyl	Nitrobenzene	12·68	6·05	3·16	0·713	1·9	2·0
"	Chlorobenzene	"	"	"	"	0·9	0·8

The following solvent dimensions were used in the calculations: For nitrobenzene, $A_2 = 8{\cdot}60$ $B_2 = 6{\cdot}05$, $C_2 = 4{\cdot}50$; for chlorobenzene, $A_2 = 8{\cdot}08$, $B_2 = 6{\cdot}05$, $C_2 = 3{\cdot}16$. Refractivities used other than those listed elsewhere are as follows: For carbon disulphide, $[R_L]_D = 21{\cdot}2$ cm.^{3}; for *pp'*-dichlorodiphenyl, $[R_L]_D = 60{\cdot}5$ cm.^{3}.

EXPERIMENTAL.

Materials.—The nitrobenzene was purified by distillation, and had b. p. 208—210°/760 mm. The benzene was thiophen-free, and was purified as previously recorded (Earl, Leake, and Le Fèvre, *J.*, 1948, 2269). Commercial decalin presumably contained the *cis*- and *trans*-forms, and distilled continuously between 185° and 194°. The fraction of b. p. 189—190°/758 mm. was used, and assumed to contain equal parts of these forms. The remaining solutes were purified by distillation or recrystallisation, and had the boiling points or melting points recorded in the literature.

TABLE III.

10^5w_2.	ϵ^{25}.	d_4^{25}.	$(\alpha\epsilon_2)_{w_2}$.	$(\beta d_2)_{w_2}$.
0	23·97	1·19828	—	—
	Benzene, M = 78·11.			
14,614	33·00	1·19135	−66·7	−0·474
19,197	32·69	1·18941	−66·5	−0·462
29,568	32·08	1·18462	−64·1	−0·462
37,678	31·59	1·18114	−63·2	−0·455
60,902	30·19	1·17132	−62·1	−0·443
83,446	28·95	1·16164	−60·2	−0·439
109,950	27·47	1·15060	−59·1	−0·434

whence $(\alpha\epsilon_2)_{w_2} = -67·2 + 78·9w_1$; $(\beta d_2)_{w_2} = -0·473 + 0·392w_1$; $[R_L]_D$ = 26·17 cm.³ (from $n_1^{25} = 1·49724$ and $d_4^{25} = 0·87378$).

	p-Dichlorobenzene, M = 147·01.			
12,507	23·47	1·19908	−40·1	0·064
24,196	32·87	1·20913	−45·7	0·076
25,001	32·90	1·20914	−42·8	0·074
36,598	32·41	1·20106	−42·6	0·076
62,492	31·44	1·20301	−40·5	0·076
85,479	30·26	1·20415	−43·4	0·069
104,340	29·66	1·20820	−41·3	0·076

whence $(\alpha\epsilon_2)_{w_2} = -42·7 + 7·67w_1$; $(\beta d_2)_{w_2} = -0·071 - 0·024w_1$; $[R_L]_D$ = 36·69 cm.³ (from von Auwers, *Annalen*, 1921, **422**, 160).

	*cyclo*Hexane, M = 84·16.			
12,628	33·17	1·18951	−63·4	−0·694
21,398	32·60	1·18366	−64·3	−0·683
26,901	32·28	1·18011	−62·9	−0·675
32,324	31·94	1·17689	−62·8	−0·662
50,797	30·81	1·16462	−62·2	−0·663
76,796	29·37	1·14917	−60·0	−0·639
100,380	27·94	1·13373	−60·0	−0·643

whence $(\alpha\epsilon_2)_{w_2} = -64·4 + 48·0w_1$; $(\beta d_2)_{w_2} = -0·692 + 0·577w_1$; $[R_L]_D$ = 27·72 cm.³ (from Landolt–Börnstein, "Tabellen," 1912, 1031).

10^5w_1.	ϵ^{25}.	d_4^{25}.	$(\alpha\epsilon_2)_{w_2}$.	$(\beta d_2)_{w_2}$.
	Naphthalene, M = 128·16.			
2,752	33·85	1·19765	−44·0	−0·229
6,841	33·60	1·19681	−54·4	−0·215
9,667	33·44	1·19625	−55·0	−0·210
24,303	32·77	1·19275	−49·3	−0·228
42,100	31·77	1·18857	−52·3	−0·231
74,229	30·17	1·18240	−51·2	−0·214
108,340	29·01	1·17853	−46·7	−0·186

whence $(\alpha\epsilon_2)_{w_2} = -51·3 + 23·2w_1$; $(\beta d_2)_{w_2} = -0·229 + 0·272w_1$; $[R_L]_D$ = 44·37 cm.³ (from von Auwers and Frühling, *Annalen*, 1921, **422**, 192).

	Decalin, M = 138·25.			
12,444	33·34	1·19252	−50·9	−0·483
16,377	33·09	1·19066	−53·9	−0·465
20,537	32·84	1·18897	−55·1	−0·453
31,524	32·30	1·18365	−52·9	−0·464
47,659	31·40	1·17691	−53·9	−0·448
79,595	29·79	1·16329	−52·5	−0·440
109,910	28·33	1·15062	−51·3	−0·434

whence $(\alpha\epsilon_2)_{w_2} = -53·7 + 15·9w_1$; $(\beta d_2)_{w_2} = -0·467 + 0·317w_1$; $[R_L]_D$ = 44·1 (calc. from Seyer and Barrow, *J. Amer. Chem. Soc.*, 1948, **70**, 802).

	Diphenyl, M = 154·20.			
12,115	33·35	1·19558	−50·8	−0·223
19,867	32·98	1·19428	−49·8	−0·201
21,865	32·88	1·19376	−49·8	−0·207
22,354	31·72	1·19379	−55·9	−0·201
32·951	32·34	1·19156	−49·5	−0·204
87,593	29·55	1·18065	−50·5	−0·201
101,370	29·01	1·17822	−48·9	−0·198

whence $(\alpha\epsilon_2)_{w_2} = -51·7 + 22·6w_1$; $(\beta d_2)_{w_2} = -0·215 + 0·238w_1$; $[R_L]_D$ = 52·41 (from von Auwers and Frühling, *loc. cit.*).

Measurements.—The apparatus used was that described by Calderbank and Le Fèvre (*J.*, 1948, 1949) modified as noted by Le Fèvre and Northcott (*J.*, 1949, 333). Observations on 7 solutions of each solute are given in Table III. Symbols and the method of computation are explained in *Trans. Faraday Soc.*, 1950, **46**, 1. The dielectric constant measurements were made relative to nitrobenzene, ϵ for which at 30° has been taken from Ball (*J.*, 1930, 570).

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446. *Reactions of Organic Peroxides. Part II. Reactions of αα-Dimethylbenzyl Hydroperoxide* ("*iso*Propylbenzene Hydroperoxide").

By E. G. E. HAWKINS.

Decomposition of αα-dimethylbenzyl hydroperoxide by ferrous sulphate, under the influence of various catalysts and thermally, gives rise to mixtures of 2-phenylpropan-2-ol, acetophenone, and α-methylstyrene. Oxidation with permanganate and the reaction with Grignard compounds have been studied. Oxidation of olefins, *iso*propanol, aldehydes, and ketones by the hydroperoxide has been carried out.

IT was first shown by Hock and Lang (*Ber.*, 1944, **77**, 257) that oxidation of *iso*propylbenzene by air gives rise to a hydroperoxide, $Ph{\cdot}CMe_2{\cdot}OOH$, although high concentrations of this compound were not obtained by them. Methods of improving the conversion into hydroperoxide have since been developed (Armstrong, Hall, and Quin, B.P. 610,293, 630,286; *J.*, 1950, 666). Acid decomposition of the hydroperoxide to yield phenol and acetone, and

reduction with sodium sulphite to provide 2-phenylpropan-2-ol, have also been described by Hock and Lang (*loc. cit.*).

It has now been found that on treatment with ferrous sulphate αα-dimethylbenzyl hydroperoxide is converted into a mixture of acetophenone and 2-phenylpropan-2-ol; a gas is evolved, containing a high percentage of ethane, presumably from the reaction in which acetophenone is produced. The ferrous sulphate is simultaneously oxidised to a ferric compound.

$$O + Ph\cdot CMe_2\cdot OH \longleftarrow Ph\cdot CMe_2\cdot OOH \longrightarrow Ph\cdot COMe + Me^- + {}^-OH$$
$$\downarrow$$
$$\frac{1}{2}C_2H_6$$

The ferrous sulphate decompositions of the hydroperoxides of *sec.*-butylbenzene (Part I, *J.*, 1949, 2076) and di*iso*propylbenzene (unpublished) appear to proceed in a similar manner.

Catalytic decomposition of the hydroperoxide also yields mixtures of acetophenone and alcohol, with variable proportions of α-methylstyrene produced by dehydration of the latter. The relative quantities of these constituents and the speed of decomposition appear to vary with the catalyst used.

Thermal decomposition of the hydroperoxide, with and without solvent, gives rise to the same products as the catalytic reactions.

Oxidation of the hydroperoxide with aqueous permanganate appears to follow a rather involved course. Some benzoic acid is formed, but the major products are again those given by simple catalytic decomposition, *i.e.*, acetophenone and carbinol.

Reaction with methylmagnesium iodide is vigorous and the end product is entirely α-methylstyrene. Presumably the alcohol is the initial product of reaction, and dehydration is brought about by the presence of iodine formed during the reaction. Ethylmagnesium bromide yields almost entirely a mixture of 2-phenylpropan-2-ol and α-methylstyrene indicating that the Grignard reagents act in a reducing capacity.

The hydroperoxide may act as a mild oxidising agent towards olefins in the presence of catalysts (V_2O_5, OsO_4); thus *cyclo*hexene yields the epoxide and traces of adipic acid, as well as various alcoholic and ketonic compounds which were not investigated. In the presence of vanadium pentoxide oct-1-ene also gives a small quantity of epoxide. Allyl alcohol yields polymeric products.

Oxidation of other types of organic compounds, in addition to olefins, is possible in presence of catalysts. A secondary alcohol (*iso*propanol) is oxidised to the corresponding ketone (acetone) in the presence of a variety of catalysts; 2-phenylpropan-2-ol and acetophenone are simultaneously produced, the latter representing a loss with respect to the oxidation of *iso*propanol.

$$Ph\cdot CMe_2\cdot OOH + Me_2CH\cdot OH \longrightarrow Ph\cdot CMe_2\cdot OH + Me_2CO$$

Further, aldehydes may be oxidised to the corresponding acids. In this case the reaction may proceed without a catalyst, but its presence increases the speed of reaction and allows a lower temperature to be used. In this way acetaldehyde, butyraldehyde, 2-ethylhexanal, and benzaldehyde have been smoothly oxidised; the hydroperoxide is reduced to 2-phenylpropan-2-ol.

$$Ph\cdot CMe_2\cdot OOH + R\cdot CHO \longrightarrow Ph\cdot CMe_2\cdot OH + R\cdot CO_2H$$

Attempts to oxidise acraldehyde to acrylic acid under a variety of conditions led only to polymerisation, as might be expected in the presence of an excess of peroxide.

Aliphatic ketones appear not to be oxidised very readily. Methyl ethyl ketone is converted into diacetyl only to a small extent; attempts to increase the conversion led to spontaneous decomposition of the peroxide, possibly owing to acid formation from the ketone by carbon–carbon fission.

*cyclo*Hexanone is oxidised in much less than the stoicheiometric amount to adipic acid.

It is of interest to compare the above reactions of the hydroperoxide with those of *tert.*-butyl hydroperoxide and aldehydes or ketones where, in the presence of acidic catalysts, condensation products are formed (U.S.P. 2,455,569; Dickey, Rust, and Vaughan, *J. Amer. Chem. Soc.*, 1949, **71**, 1432):

$$R\cdot CHO + CMe_3\cdot OOH \longrightarrow R\cdot CH(OH)\cdot OO\cdot CMe_3$$
$$R_2CO + 2CMe_3\cdot OOH \longrightarrow R_2C(OO\cdot CMe_3)_2 + H_2O$$

Experimental.

M. p.s are uncorrected, and elementary analyses are by Drs. Weiler and Strauss. Analyses of the peroxide decomposition products—2-phenylpropan-2-ol, acetophenone, and α-methylstyrene mixtures—were generally carried out by infra-red absorption spectroscopy by using the method of matching with synthetic mixtures (Philpotts and Thain, forthcoming publication).

2-Phenylpropan-2-ol.—For comparative purposes, and as a standard for infra-red analyses, a pure sample of the alcohol was prepared from acetophenone and methylmagnesium iodide in the normal manner. It had b. p. *ca.* 90°/15 mm. and, after three recrystallisations from light petroleum, m. p. 33—34° (Found: C, 79·4; H, 9·0. Calc. for $C_9H_{12}O$: C, 79·4; H, 8·8%).

Reactions of αα-Dimethylbenzyl Hydroperoxide.—Ferrous sulphate. Hydroperoxide (29·5 g.) and ferrous sulphate (45 g. in 100 c.c. of water) were shaken together; the mixture became warm. Gas was evolved; a portion, on analysis, was found to contain 72·5% of ethane. The product was worked up in the normal manner and finally distilled; the bulk of the distillate (13·5 g.) had b. p. 180—200°, and contained acetophenone (8·6 g.; identified by its 2 : 4-dinitrophenylhydrazone); infra-red analysis showed the remainder to be 2-phenylpropan-2-ol.

Catalytic decomposition. (i) Hydroperoxide (20 g.) in heptane (50 g.) containing a trace of vanadium pentoxide was heated at 110—120° for 16 hours before decomposition was complete. Distillation provided, apart from the heptane, material (17·2 g.), b. p. *ca.* 96°/25 mm., and a residue (1·7 g.). Infra-red analysis of the distillate showed it to consist of 2-phenylpropan-2-ol (53%), acetophenone (29%), and α-methylstyrene (13%).

(ii) Experiment (i) was repeated, but the vanadium pentoxide was replaced by osmium tetroxide (2 c.c. of a 1% solution in *tert.*-butanol). Decomposition was complete in 4 hours. Distillation provided heptane and a product (13·3 g.), b. p. 60—90°/20 mm., as well as a residue (1·8 g.). Infra-red analysis showed the distillate to contain acetophenone (11%) and α-methylstyrene (86%), but no carbinol.

(iii) Hydroperoxide (10 g.) and manganese naphthenate (0·1 g.) were heated on the water-bath for 6 hours; >90% of the peroxide had decomposed during the first 2 hours. Distillation yielded the product (8·5 g.), b. p. 90—100°/20—25 mm., and a residue (0·8 g.). The product contained carbinol (75%), acetophenone (19·5%), and α-methylstyrene (*ca.* 1%).

Thermal decomposition. (i) Hydroperoxide (10 g.) in *iso*propylbenzene (25 g.) was heated at 140—150° (bath-temp.) for 11 hours before complete decomposition occurred. The distillate (14·0 g.), b. p. 80—83°/15 mm., contained the propanol (73%), acetophenone (21%), and α-methylstyrene (0·7%).

(ii) Hydroperoxide (20 g.) was slowly dropped (1 hour) through a tube packed with broken porcelain and heated to 200—220°; the product passed through a condensing system. The collected material (17·5 g.) smelt strongly of formaldehyde. It was dissolved in light petroleum, and the solution dried and distilled to give fractions (1) (trace), b. p. <60°, (2) (13·0 g.), b. p. 185—195°, (3) (1·1 g.), b. p. 110—150°/15 mm., and a residue (1·2 g.).

Fraction 1 smelt strongly of formaldehyde, the presence of which was confirmed by formation of its 2 : 4-dinitrophenylhydrazone. Fraction 2 contained phenol (3·7%), and by infra-red analysis, the propanol (2%), acetophenone (70%), and α-methylstyrene (10%). Fraction 3 was similarly shown to contain mainly acetophenone, but also a little carbinol and α-methylstyrene.

Oxidation. Potassium permanganate (30 g.) in water (250 c.c.) was stirred at 30°, and hydroperoxide (20 g.) added dropwise. Manganese dioxide formed during the reaction was filtered off; the filtrate was acidified and extracted with ether. After removal of solvent the product on distillation gave fractions (1) (9·0 g.), b. p. 88—100°/15 mm., (2) (4·3 g.), b. p. 100—128°/15 mm., and a residue (1·2 g.). Fraction 1, according to infra-red analysis, contained the propanol (66%) and acetophenone (25·5%), but no α-methylstyrene. Fraction 2 contained the propanol (33·5%), acetophenone (41·7%), and benzoic acid (13·0%; crystals of this separated on storage).

Methylmagnesium iodide. Hydroperoxide (20 g.) was gradually added to the Grignard reagent from methyl iodide (60 g.). A vigorous reaction took place in which some iodine appeared to be liberated. The product was worked up in the normal way. Distillation led to some dehydration; the product (8·2 g.) had b. p. 145—155°, and left a residue (1·2 g.). The distillate contained some free iodine. Infra-red analysis showed the distillate to consist of α-methylstyrene (97%), with no appreciable quantity of carbinol or acetophenone.

Ethylmagnesium bromide. The reaction of hydroperoxide (20 g.) with the Grignard reagent from ethyl bromide (50 g.), carried out as above, yielded as product a mixture (14·8 g.) shown by infra-red analysis to consist almost entirely of 2-phenylpropan-2-ol (60%) and α-methylstyrene (32%).

cyclo*Hexene.* (i) Hydroperoxide (25 g.) and *cyclo*hexene (50 g.) containing a trace of vanadium pentoxide were heated on the water-bath for 2 hours, and then under reflux on an oil-bath for 17 hours before the peroxide had completely disappeared. Distillation yielded unchanged olefin and fractions, b. p. 90—150° (2·5 g.), b. p. 150—170° (7·4 g.), and b. p. 94—98°/16 mm. (19·0 g.), and a residue (2·9 g.). The last fraction was 2-phenylpropan-2-ol formed by reduction of the hydroperoxide (Found: Active H, 0·73%. Calc. for $C_9H_{12}O$: 0·74%). The first two fractions were combined and redistilled to yield mainly material (6·3 g.), b. p. 130—134°, n_D^{20} 1·4543 (epoxide content, 94%, calc. as *cyclo*hexene epoxide; Nicolet and Poulter, *J. Amer. Chem. Soc.*, 1930, **52**, 1186). Treatment with warm dilute sulphuric acid, followed by extraction with ether, provided *cyclo*hexane-1 : 2-diol, m. p. 100—102°, undepressed on admixture with an authentic specimen.

(ii) Hydroperoxide (13 g.) in *cyclo*hexene (8·5 g.) was added gradually, with shaking, to *cyclo*hexene (13 g.) containing osmium tetroxide (1 c.c. of 0·5% solution). The reaction was exothermic and external cooling had to be applied. At the end of the addition no free peroxide remained and the solution was

distilled. Only small quantities of oxidation products of *cyclo*hexene were formed; these distilled with the 2-phenylpropan-2-ol (from the hydroperoxide) and could not be easily separated from it. A *p*-nitrophenylhydrazone, m. p. 244—248° (decomp.), was isolated; its analysis agreed with that expected of a bis-derivative from a cyclic C_6-diketone (Found: C, 56·6; H, 4·9; N, 22·0. Calc. for $C_{18}H_{18}O_4N_4$: C, 56·5; H, 4·7; N, 22·0%.

No epoxide was isolated in this experiment, but from the residue was obtained a trace of slightly impure adipic acid, m. p. 147—148° (mixed m. p. undepressed) (Found: equiv., 79. Calc. for $C_6H_{10}O_4$: equiv., 73).

Oct-1-ene. Hydroperoxide (25 g.) and oct-1-ene (25 g.), containing a trace of vanadium pentoxide, were heated at *ca.* 120° for 11½ hours, decomposition of the peroxide being then complete. After removal of unchanged octene distillation at 22 mm. provided fractions boiling from 70° to 105°. These consisted mainly of 2-phenylpropan-2-ol, but contained 3·1 g. of epoxide (calc. as 1 : 2-epoxy-octane; Nicolet and Poulter, *loc. cit.*). The product was not further examined.

Allyl alcohol. (i) Hydroperoxide (30 g.) and allyl alcohol (20 g.) were heated on the water-bath for *ca.* 30 hours for complete disappearance of peroxide. Distillation yielded 2-phenylpropan-2-ol (24·5 g.), b. p. 94°/16 mm., and a residue of brown gummy resin (14·5 g.).

(ii) The same quantities as in (i) being used, the hydroperoxide was added gradually, with shaking and cooling, to the alcohol containing osmium tetroxide (0·2 c.c. of 0·5% solution). The reaction was complete at the end of the addition. Distillation again gave only the propanol (24·2 g.) and left a resin (11·0 g.).

*iso*Propanol. The hydroperoxide (20 g.) and *iso*propanol (30 g.) containing a trace of catalyst were heated to gentle ebullition (bath-temp. 120°). Liquid was allowed to distil off slowly through a short (1 ft.) packed column. Fresh *iso*propanol was added at the same rate as liquid distilled. Acetone produced was determined by titration of portions of the distillate, and the heating continued until the peroxide had completely decomposed. The *iso*propanol was then removed, and the residue distilled and analysed by the infra-red method; it was found to contain varying proportions of the propanol, acetophenone, and α-methylstyrene, but no phenol except when chromic oxide was used as catalyst (see following table).

Catalyst.	Time (hrs.).	Acetone produced (g.).	Catalyst.	Time (hrs.).	Acetone produced (g.).
V_2O_5	4½	2·84	CrO_3	8	5·05 *
OsO_4	—	2·71	$Al(OPr^i)_3$	1 week	3·53
MnO_2	16	3·83	Mn naphthenate	15	1·96
WO_3	15	2·96	Co naphthenate	20	2·4

* Crude residue contained phenol, and presumably part of the acetone produced was due to slight acid decomposition of the peroxide.

Acetaldehyde. (i) Hydroperoxide (5 g.) was gradually added to acetaldehyde (6 g.) at $<-10°$. After 3 hours very little of the peroxide had reacted.

(ii) Acetaldehyde (12 g.) was slowly added to hydroperoxide (10 g.), containing a trace of osmium tetroxide solution, the mixture being cooled below −10°. After 3 hours the peroxide had completely reacted and titration indicated the presence of acetic acid (3·58 g., *ca.* 92% calc. on the peroxide). Distillation gave acetic acid (3·49 g.) and a mixture of the propanol (60%), acetophenone (15%), and α-methylstyrene (25%).

Butyraldehyde. (i) Hydroperoxide (92·5%; 10 g.) was added slowly to butyraldehyde (8 g.) cooled below 0°. After ½ hour at room temperature very little reaction had taken place; the mixture was heated at 40—50° for ½ hour, then at 90—100° for 2½ hours, before complete peroxide decomposition had occurred. The butyric acid formed was 5·09 g. (by titration), *i.e.*, 95% calc. on peroxide. Distillation provided butyric acid (4·47 g.) and 2-phenylpropan-2-ol (free from acetophenone).

(ii) The experiment was repeated at 90—100° throughout. Reaction was complete in 3 hours. The yield of butyric acid (by titration) was 90%.

(iii) Hydroperoxide (20 g.) and butyraldehyde (13·9 g.), containing a trace of vanadium pentoxide, were heated at 110° for 3 hours. The butyric acid formed was 8·9 g. (77%; by titration). After removal of the acid by alkali the residue yielded a distillate (15 g.), b. p. 70—80°/15 mm., and a residue (1·3 g.), the former containing the propanol (85%) and acetophenone (13%), but no α-methylstyrene.

(iv) Hydroperoxide (10 g.) and butyraldehyde (8 g.) containing osmium tetroxide (1 c.c. of 1% solution) were allowed to react at 0° and then kept overnight at room temperature; the peroxide had completely reacted. Titration showed the presence of 3·84 g. of butyric acid; distillation yielded butyric acid (3·66 g.) and a fraction (7·9 g.) containing the propanol (77%) and acetophenone (14%), but no α-methylstyrene.

(v) Hydroperoxide (10 g.) was gradually added, with stirring, to a mixture of butyraldehyde (8 g.) and methanol (22 g.) containing osmium tetroxide (1 c.c.; 1% solution) at −10° to −15°. After being kept overnight at room temperature the solution was heated at 80° for 5 hours. Titration showed the presence of butyric acid (5·65 g., 97·6%).

2-*Ethylhexanal.* Hydroperoxide (10·6 g.) was gradually added to 2-ethylhexanal (12·0 g.) containing osmium tetroxide (1 c.c.; 1% solution), the temperature being kept below −10°. After 4 hours 10% of the hydroperoxide remained unchanged, but next morning the reaction was complete. The 2-ethylhexanoic acid formed (10·4 g.) yielded a *p*-bromophenacyl ester, m. p. 94—98°. After removal

of the acid by alkali the residue contained the propanol (72%) and a mixture (15—20%) of acetophenone and ethylhexanal.

Benzaldehyde. Hydroperoxide (5 g.) was added to freshly distilled benzaldehyde (5 g.), containing osmium tetroxide, at 0°. Reaction was complete in 1½ hours; benzoic acid (4·65 g., 91%, calc. on peroxide) and a mixture of (mainly) the propanol and acetophenone were produced. Benzoic acid, m. p. 121°, was regenerated from the alkali washings of the reaction product.

Acraldehyde. Several attempts were made to oxidise acraldehyde with the hydroperoxide, using an osmium tetroxide catalyst and in the presence of various antipolymerisation catalysts, *e.g.*, sulphur, tannic acid, but in every case polymerisation set in during the course of the oxidation; the temperature became out of control at this point.

Methyl ethyl ketone. Hydroperoxide (30 g.) and methyl ethyl ketone (15 g.) were heated at a bath-temp. of *ca.* 100°. The solution gradually became slightly yellow, but after 7 hours it became black and a rapid decomposition had set in. Distillation provided unchanged ketone containing traces of diacetyl (gave nickel-dimethylglyoxime), but the higher-boiling material (b. p. *ca.* 180°; 11·3 g.) was phenol, which crystallised on storage. A black residue (9·5 g.) remained.

*cyclo*Hexanone. Hydroperoxide (10 g.) and *cyclo*hexanone (4 g.) were heated together for 2 hours at 100—110° but very little decomposition of the peroxide occurred. Copper naphthenate was added and heating continued for a further 7 hours before complete destruction of the peroxide occurred. Titration showed the presence of 1·2 g. of acid (as adipic acid). Unchanged *cyclo*hexanone (1·87 g.) and decomposition products of the peroxide (6·2 g.) were removed by distillation, and the residue was extracted with boiling water. A little adipic acid, m. p. 150°, undepressed on admixture with an authentic sample, crystallised from the aqueous extract.

The author acknowledges his indebtedness to Messrs. A. R. Philpotts and W. Thain for carrying out the infra-red analyses and to Mr. B. E. V. Bowen for the gas analyses. Thanks are also offered to the Directors of the Distillers Company Limited for permission to publish this paper.

The Distillers Company Limited,
Research and Development Department,
Great Burgh, Epsom.

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447. *Synthetic Analgesics and Related Compounds. Part I. Amidines and 4 : 5-Dihydroglyoxalines.*

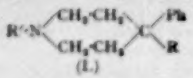
By Walter Wilson.

Several cyano-compounds related to amidone and pethidine have been converted into the corresponding *N*-phenylamidines and 4 : 5-dihydroglyoxalines. Tertiary cyanides were abnormally unreactive. The cyanide (II; R = CN), an intermediate in the production of amidone, with 2-aminoethylammonium toluene-*p*-sulphonate at 200° afforded a 2-imino-pyrrolidine and not the expected 4 : 5-dihydroglyoxaline.

The conversion, into amidines and 4 : 5-dihydroglyoxalines, of various cyano-compounds related to pethidine (I; R = CO_2Et, R′ = Me) and amidone (II; R = COEt) has been studied, fusion techniques (cf., especially, Oxley and Short, *J.*, 1946, 147; 1947, 497) being used. The present experiments have been restricted mainly to reaction with anilinium arylsulphonates (giving *N*-phenylamidines) and 2-aminoethylammonium toluene-*p*-sulphonate (giving 2-substituted 4 : 5-dihydroglyoxalines) at 200°. Basic cyanides were used as their salts with benzenesulphonic or toluene-*p*-sulphonic acid.

Improved methods for preparing benzhydryl cyanide have recently been described (Reid and Turner, *J. Amer. Chem. Soc.*, 1948, **70**, 3515; U.S.P., 2,447,419; Ginsburg and Baizer, *J. Amer. Chem. Soc.*, 1949, **71**, 2254). The material used in the present work was obtained by boiling diphenylacetamide with thionyl chloride (cf. Freeman, Ringk, and Spoerri, *ibid.*, 1947, **69**, 858), yields being satisfactory if the time of heating was not prolonged. Long heating gave large amounts of α-chlorobenzhydryl cyanide (IV; R = CN, R′ = Cl), identified by acid hydrolysis to benzophenone cyanohydrin (IV; R = CN, R′ = OH). An attempt to convert the chloro-cyanide into the anilino-cyanide (Miller, Plöchl, and Rohde, *Ber.*, 1892, **25**, 2056) afforded only aniline hydrochloride and benzophenone. The mechanism of formation of the chloro-cyanide remains obscure. Pure benzhydryl cyanide gave only traces of the chloro-cyanide on prolonged boiling with pure thionyl chloride, and the reaction was not catalysed by small amounts of iodine, red phosphorus, ammonium chloride, or ferric chloride. It is possible that, under appropriate conditions, thionyl chloride behaves as a chlorinating reagent by decomposing as follows (cf. sulphuryl chloride and peroxide catalysts, Kharasch and Brown,

J. Amer. Chem. Soc., 1939, **61**, 2142; also Patai and Bergmann, *ibid.*, 1950, **72**, 1034): $2SOCl_2 \longrightarrow 2SO + 2Cl \longrightarrow S + SO_2 + 2Cl$.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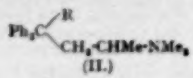
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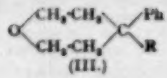
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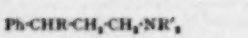
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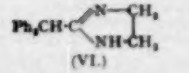
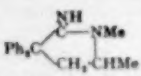
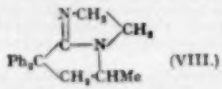

(VI.)

Benzhydryl cyanide (IV; R = CN, R′ = H) readily afforded both the *N*-phenylamidine and the 4 : 5-dihydroglyoxaline (VI) (cf. Jílek and Protiva, *J.*, 1950, 188). The tertiary cyanide (IV; R = CN, R′ = Et) did not react with amine salts under the conditions used; the allyl analogue (IV; R = CN, R′ = CH_2·CH:CH_2) also failed to react with ethylenediamine salts.

The tetrahydropyran (III; R = CN) and two cyanides (I; R = CN, R′ = Me or CH_2Ph) of pethidine type were converted in good yields into the 2-substituted 4 : 5-dihydroglyoxalines on prolonged heating with ethylenediamine salts. The tetrahydropyran (III; R = CN) gave heterogeneous melts with ammonium or anilinium benzenesulphonates, which may account for the non-formation of amidines. Conversion of the other two cyanides into amidines was not examined.

The expected *N*-phenylamidines and 4 : 5-dihydroglyoxalines were easily prepared from the two basic cyanides (V; R = CN, R′ = Me or Et) obtained by aminoalkylation of benzyl cyanide. However, similar but tertiary basic cyanides derived from benzhydryl cyanide were unreactive. Thus 3-dimethylamino-1-cyano-1 : 1-diphenylpropane (as the toluene-*p*-sulphonate) was unchanged on heating (200°) with 2-aminoethylammonium toluene-*p*-sulphonate. The homologous (±)-cyanide (II; R = CN) was converted in moderate yield into a basic compound, m. p. 103°, which was not, however, the dihydroglyoxaline. The stereoisomeric (+)-cyanide (II; R = CN) similarly afforded the dextro-rotatory isomer, believed to be 2-imino-3 : 3-diphenyl-1 : 5-dimethylpyrrolidine (VII). Evidently, the ethylenediamine used does not enter into the composition of this molecule. Similar compounds have been obtained by heating salts of basic cyanides of the amidone series (Blicke and Zambito, Abstr. 111th Meeting Amer. Chem. Soc., 1947, 3K). An alternative structure (VIII) for the compound of m. p. 103° was considered improbable in view of the formation of the dextrorotatory isomer: during the formation of (VIII) racemisation would be expected.

(VII.) 


(VIII.)

Abnormal or particularly ready cyclisations affording five-membered ring compounds for *gem*-diphenyl compounds have been commented on elsewhere (Schultz, Robb, and Sprague, *J. Amer. Chem. Soc.*, 1947, **69**, 2454; Wilson, *J.*, 1948, 1993; Clarke, Mooradian, Lucas, and Slauson, *J. Amer. Chem. Soc.*, 1949, **71**, 2821; Walton, Ofner, and Thorpe, *J.*, 1949, 648; Dupré, Elks, Hems, Speyer, and Evans, *J.*, 1949, 500). Experiments are proceeding on the independent synthesis of compounds of types (VII) and (VIII).

The resistance to amidine and 4 : 5-dihydroglyoxaline formation shown by the tertiary cyanides was possibly caused by steric factors. Normal reactions were observed only with those tertiary cyanides in which the α-carbon atom was contained in a piperidine or tetrahydropyran ring.

The compounds prepared in this work, which combine features of the potent synthetic analgesics with the amidine and 4 : 5-dihydroglyoxaline groups, are being assayed for biological activity. No outstanding activity has as yet been observed.

Experimental.

α-Chlorobenzhydryl Cyanide.—Boiling diphenylacetamide for 5—8 hours with excess of thionyl chloride gave satisfactory yields of benzhydryl cyanide (Reid and Turner, *J. Amer. Chem. Soc.*, 1948, **70**, 3515; Freeman, Ringk, and Spoerri, *ibid.*, 1947, **69**, 858). After prolonged boiling (30 hours), however, the product contained about 40% of an oil. Removal of benzhydryl cyanide by low-temperature crystallisation from light petroleum (b. p. 40—60°) and distillation of the soluble fraction

gave evil-smelling *α-chlorobenzhydryl cyanide*, b. p. 140°/1 mm. (Found: N, 6·15; Cl, 14·7. $C_{14}H_{10}NCl$ requires N, 6·15; Cl, 15·6%).

Hydrolysis. The foregoing chloro-compound was boiled with water for 2½ hours. The resulting unstable benzophenone cyanohydrin recrystallised from light petroleum (b. p. 40—60°) as white crystals, m. p. 120°. The product gave an intense red colour with concentrated sulphuric acid and was immediately hydrolysed by cold dilute sodium hydroxide to hydrogen cyanide and benzophenone (2 : 4-dinitrophenylhydrazone, m. p. 239°) (cf. Wittig and Pockels, *Ber.*, 1936, **69**, 790).

4-Cyano-4-phenyl-1-benzylpiperidine (I; R = CN; R′ = CH_2Ph).—This was prepared by the I.G.Farbenind. (Hoechst) process (B.I.O.S. Final Report No. 766, p. 62; Eisleb, *Ber.*, 1941, **74**, 1433). The *benzenesulphonate* formed needles (from *iso*propanol), m. p. 194—195° (Found: N, 6·6. $C_{25}H_{24}O_2N_2S$ requires N, 6·45%).

Benzyldi-(2-chloroethyl)amine.—A toluene solution of the chloro-amine (described by Eisleb, *loc. cit.*) was used in the above process. Such solutions were conveniently assayed by adding saturated methanolic picric acid and weighing the insoluble *picrate*. This formed yellow prisms, m. p. 129·5—130·5°, from acetone (Found: N, 12·15. $C_{17}H_{18}O_7N_4Cl_2$ requires N, 12·2%).

Alcoholysis of 4-Cyano-4-phenyl-1-benzylpiperidine.—The cyanide (56·3 g.), water (6 c.c.) and sulphuric acid (28·5 c.c.) were heated alone and then with slow addition of absolute ethanol (cf. *op. cit.*, p. 62). The crude product (46 g.) was recrystallised from water and identified as *4-phenyl-1-benzylpiperidine-4-carboxyamide hydrochloride*, prisms, m. p. 275° (Found: N, 8·0; Cl, 10·1. $C_{19}H_{23}ON_2Cl$ requires N, 8·5; Cl, 10·7%).

Authentic 4-Phenyl-1-benzylpiperidine-4-carboxyamide.—The 4-carboxylic acid (Eisleb, *loc. cit.*) (5 g.) was heated with excess of thionyl chloride and then mixed with aqueous ammonia (*d* 0·88). The impure amide (1·9 g.; m. p. 92—97°) was filtered off and converted by hydrogen chloride in glacial acetic acid into the hydrochloride, white prisms (from acetone), m. p. 276°, not depressed on admixture with the material from the previous experiment (Found: N, 8·5%). Acidification of the ammoniacal mother-liquors gave some unchanged acid (1·7 g.).

3-Dialkylamino-1-cyano-1-phenylpropanes (V; R = CN).—The 3-dimethylamino-compound was obtained from 2-dimethylaminoethyl chloride and benzyl cyanide (Clarke, Mooradian, Lucas, and Slauson, *J. Amer. Chem. Soc.*, 1949, **71**, 2821) and converted into the *toluene-p-sulphonate*, m. p. 111° (from *iso*propanol–ether) (Found: N, 7·55. $C_{19}H_{24}O_3N_2S$ requires N, 7·8%). The 3-diethylamino-analogue (Eisleb, *loc. cit.*; Heilbron, Cook, and Brown, *J.*, 1949, S106) similarly gave a *toluene-p-sulphonate*, m. p. 105° (Found: C, 64·95; H, 7·1. $C_{21}H_{28}O_3N_2S$ requires C, 65·0; H, 7·25%).

3-Dimethylamino-1-cyano-1 : 1-diphenylpropane.—The base (Dupré, Elks, Hems, Speyer, and Evans, *J.*, 1949, 500) with toluene-*p*-sulphonic acid monohydrate (1 mole) in *iso*propanol afforded the *toluene-p-sulphonate*, m. p. 174—175° (74%) (Found: C, 68·9; H, 6·2. $C_{24}H_{27}O_3N_2S$ requires C, 68·8; H, 6·4%).

(±)-*3-Dimethylamino-1-cyano-1 : 1-diphenylbutane* (II; R = CN).—The base has been adequately described (Bockmühl and Ehrhart, *Annalen*, 1948, **561**, 52; also Schultz, Robb, and Sprague, *J. Amer. Chem. Soc.*, 1947, **69**, 2454; Attenburrow, Elks, Hems, and Speyer, *J.*, 1949, 510). By use of a 5% excess of hydrated benzenesulphonic acid in acetone–ethyl acetate, the *benzenesulphonate* was obtained (65%). Crystallised from acetone–ethyl acetate, this had m. p. 158—159° (Found: N, 6·55. $C_{25}H_{28}O_3N_2S$ requires N, 6·4%).

(+)-*3-Dimethylamino-1-cyano-1 : 1-diphenylbutane.*—The (±)-cyanide was resolved with tartaric acid (Walton, Ofner, and Thorpe, *J.*, 1949, 652; Buck *et al.*, *J. Amer. Chem. Soc.*, 1948, **70**, 4195). The (+)-cyanide was converted into the (+)-*toluene-p-sulphonate* in acetone. Crystallised from methanol–ether, this had m. p. 154° (Found: N, 6·5. $C_{25}H_{28}O_3N_2S$ requires N, 6·4%).

N-Phenyldiphenylacetamidine.—Heating benzhydryl cyanide (7·6 g.) and anilinium benzenesulphonate (10 g.) at 195—200° for 4 hours, trituration with acetone, and recrystallisation of the product (13·5 g., 76%; m. p. 164—167°) from *iso*propanol–ether gave the *amidinium benzenesulphonate*, m. p. 174—176° (Found: N, 6·3. $C_{33}H_{32}O_3N_2S$ requires N, 6·3%).

Warm dilute ammonia precipitated the free *amidine* (7·2 g.; m. p. 156°), crystallising from aqueous methanol in minute needles, m. p. 150° (Found: N, 9·8. $C_{27}H_{24}N_2$ requires N, 9·8%). After 16 hours in the air the crude material (initial m. p. 156°) had m. p. 141—149° (shrinking at 135°). Crystallisation failed to restore the material to its original m. p. The dry material became electrically charged when ground with a spatula.

2-Benzhydryl-4 : 5-dihydroglyoxaline (cf. Jílek and Protiva, *loc. cit.*).—Benzhydryl cyanide (1·9 g.) and 2-aminoethylammonium toluene-*p*-sulphonate (2·3 g.) were heated at 200° for 3½ hours and the base (2·05 g.) was precipitated by aqueous ammonia. It crystallised from aqueous methanol in needles, m. p. 143—145° (Found: N, 12·05. Calc. for $C_{18}H_{16}N_2$: N, 11·9%). Jílek and Protiva, *loc. cit.*, give m. p. 133—135°; Aspinall, *J. Amer. Chem. Soc.*, 1939, **61**, 3195, gives 137°. The hydrochloride formed prisms (from ethanol), m. p. 182°, resolidifying with change of crystalline form and remelting at 197° (Found: N, 9·85. Calc. for $C_{18}H_{17}N_2Cl$: N, 10·25%) (Jílek and Protiva, *loc. cit.*, give m. p. 180—182°; Ciba, Austrian P. 150,307, give 192—193°).

Reaction Between 1-Cyano-1 : 1-diphenylpropane and 2-Aminoethylammonium Toluene-p-sulphonate.—The benzhydryl cyanide in the previous experiment was replaced by 1-cyano-1 : 1-diphenylpropane (2·2 g.) (b. p. 158—162°/2 mm.; Ramart-Lucas, *Ann. Chim.*, 1913, [viii], **30**, 417; Klingemann, *Annalen*, 1893, **275**, 86). The minute yield of base was recrystallised from aqueous ethanol, affording 2-benzhydryl-4 : 5-dihydroglyoxaline (0·2 g.), m. p. 140° not depressed on admixture with an authentic specimen (Found: N, 12·2%).

4-*Phenyl*-4-(4 : 5-*dihydroglyoxalin*-2-*yl*)*tetrahydropyran* (III ; R = dihydroglyoxalin-2-yl).—4-Cyano-4-phenyltetrahydropyran (7·6 g.) (Eisleb, *loc. cit.*) and 2-aminoethylammonium toluene-*p*-sulphonate (9·2 g.) were heated at 200° for 14 hours, then cooled, and triturated with acetone. The solid (13 g., 90·5%; m. p. 260°) on recrystallisation from water afforded the pure ***dihydroglyoxalinium toluene-p-sulphonate*** as white needles, m. p. 263—264° (Found : N, 6·6. $C_{21}H_{24}O_4N_2S$ requires N, 6·95%). The salt was dissolved in water, excess of sodium hydroxide added (no precipitate), and the base (6·1 g.; m. p. 125—128°) isolated by extraction with chloroform. It was converted directly into the ***hydrochloride***, small prisms (from acetone–ethanol), m. p. 247—248° (Found : N, 10·5. $C_{14}H_{19}ON_2Cl$ requires N, 10·5%).

4-*Phenyl*-4-(4 : 5-*dihydroglyoxalin*-2-*yl*)-1-*methylpiperidine* (I ; R = dihydroglyoxalin-2-yl ; R′ = Ph).—4-Cyano-4-phenyl-1-methylpiperidine (10 g.) (Eisleb, *loc. cit.*) in methanol–ethyl acetate afforded the ***benzenesulphonate*** (12·9 g.), prisms, m. p. 168—168·5° (Found : N, 7·95. $C_{19}H_{22}O_3N_2S$ requires N, 7·8%). This salt (3·6 g.) and 2-aminoethylammonium toluene-*p*-sulphonate (2·3 g.), heated at 200° for 15 hours and then triturated with acetone, gave a salt (4·2 g.; m. p. 245—260°), which was dissolved in water, basified with sodium hydroxide, and extracted with chloroform, to afford a base (1·5 g.; m. p. 112—114°) which could not be satisfactorily recrystallised. The ***dihydrochloride*** crystallised from ethanol–ether in small prisms, m. p. 336—337° (Found : N, 13·7. $C_{14}H_{20}N_2Cl_2$ requires N, 13·3%).

4-*Phenyl*-1-*benzyl*-4-(4 : 5-*dihydroglyoxalin*-2-*yl*)*piperidine* (I ; R = dihydroglyoxalin-2-yl ; R′ = Me).—4-Cyano-4-phenyl-1-benzylpiperidinium benzenesulphonate (4·3 g.) and 2-aminoethylammonium toluene-*p*-sulphonate (2·3 g.) after 31 hours at 200° afforded a crude salt (3·0 g.; m. p. 171—175°), which was dissolved in water and basified with sodium hydroxide. The solid precipitate (1·3 g.; m. p. 153—154°) was recrystallised from aqueous ethanol. The ***dihydroglyoxaline*** formed prisms, m. p. 155—156° (Found : N, 13·2. $C_{21}H_{25}N_3$ requires N, 13·1%); the ***dihydrochloride***, crystallised from methanol–ether, had m. p. 215—218° (Found : N, 10·8. $C_{21}H_{27}N_3Cl_2$ requires N, 10·7%).

5-Dialkylamino-N : 2-diphenylbutyramidines.—3-Dimethylamino-1-cyano-1-phenylpropane toluene-*p*-sulphonate (2·7 g.) and anilinium toluene-*p*-sulphonate (2·7 g.) were heated for 6½ hours at 200°, dissolved in water, and treated with aqueous ammonia to give a base (1·95 g.), m. p. 114—116°. Recrystallisation from benzene–light petroleum (b. p. 100—120°) afforded the ***5-dimethylamino-amidine*** as small pearly needles, m. p. 123·5—124° (Found : C, 77·05; H, 8·5. $C_{18}H_{21}N_3$ requires C, 77·0; H, 8·2%). Similarly, 3-diethylamino-1-cyano-1-phenylpropane toluene-*p*-sulphonate (3·9 g.) was converted into the ***5-diethylamino-amidine*** (1·2 g.), small crystals [from benzene–light petroleum (b. p. 100—120°)], m. p. 104·5—15·5° (Found : C, 77·6; H, 8·8. $C_{22}H_{31}N_3$ requires C, 77·8; H, 8·75%).

2-(3-*Dialkylamino*-1-*phenylpropyl*)-4 : 5-*dihydroglyoxalines.*—3-Dimethylamino-1-cyano-1-phenylpropane toluene-*p*-sulphonate (3·6 g.) and 2-aminoethylammonium toluene-*p*-sulphonate (2·3 g.), heated at 200° for 7 hours and then triturated with acetone, gave a salt (2·95 g.; m. p. 223—224°). After recrystallisation from aqueous ethanol, the ***3′-dimethylaminoditoluene-p-sulphonate*** formed needles, m. p. 233—234° (Found : C, 58·5; H, 6·3. $C_{32}H_{37}O_6N_3S_2$ requires C, 58·4; H, 6·4%). The free base was an oil.

Similarly, 3-diethylamino-1-cyano-1-phenylpropane toluene-*p*-sulphonate (3·9 g.) afforded the ***3′-diethylamino-ditoluene-p-sulphonate*** (3·2 g.), prisms m. p. 127°, from *iso*propanol–ether (Found : C, 58·85, 59·0; H, 6·6, 6·8. $C_{30}H_{41}O_6N_3S_2$ requires C, 59·7; H, 6·8%). The free base was an oil.

Reaction between (±)-***3-Dimethylamino*-1-*cyano*-1 : 1-*diphenylbutane and Ethylenediamine.***—The (±)-cyanide benzenesulphonate (11 g.) and 2-aminoethylammonium toluene-*p*-sulphonate (5·8 g.) were heated at 200° for 27½ hours. Trituration with cold acetone gave a crystalline salt (2·75 g.; m. p. 184—189°), which was dissolved in water; the base (1·5 g.; m. p. 100—102°) was precipitated by aqueous sodium hydroxide. Several crystallisations from aqueous methanol afforded (±)-***2-imino*-3 : 3-*diphenyl*-1 : 5-*dimethylpyrrolidine*** as prisms, m. p. 103°, becoming white and opaque when dry (Found : C, 82·3; H, 7·5; N, 10·1. $C_{18}H_{20}N_2$ requires C, 81·9; H, 7·6; N, 10·6%). The compound was not acetylated by acetic anhydride in pyridine and was largely recovered unchanged after prolonged boiling with concentrated hydrochloric acid, or with potassium hydroxide in ethylene glycol.

Reaction between the (+)-***Cyanide and Ethylenediamine.***—The above reaction was repeated with the dextrorotatory cyanide. The resultant crude salt (2 g.; m. p. 150—160°) was converted into the (+)-pyrrolidine (1·3 g.), which crystallised from aqueous methanol in needles, m. p. 130°; $[\alpha]_D^{17}$ +157° (*c*, 1·29 in methanol) (Found : C, 82·1; 82·4; H, 6·95; 7·05; N, 10·75%). The compound was unchanged after treatment with acetic anhydride in pyridine.

The author is indebted to Dr. D. A. Peak for valuable discussion and particularly for suggesting the initial experiment in this series.

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448. *Magnetochemistry of the Heaviest Elements. Part I. A Sensitive Magnetic Susceptibility Balance for Small Samples.*

By J. K. Dawson and M. W. Lister.

A balance is described by means of which magnetic susceptibilities may be measured on milligram amounts of solids by using a modification of the Faraday method. With a maximum field strength of about 2500 gauss, the susceptibility of a 10-mg. sample of specific susceptibility 1×10^{-6} is measurable to 0·5%. The balance is convenient for general susceptibility measurements even when larger amounts are available.

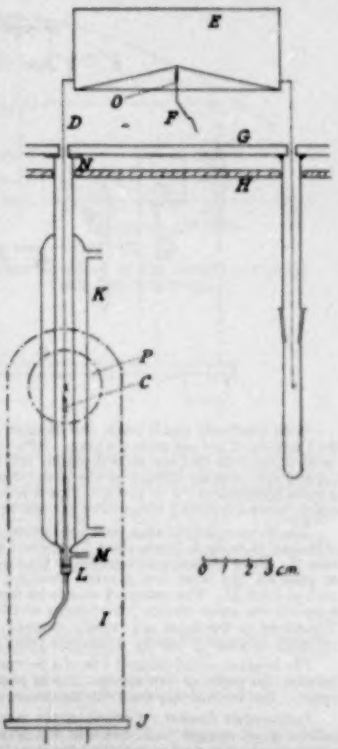
Investigation of the magnetic properties of compounds of the elements beyond actinium calls for the development of a balance for use with samples of the order of a milligram. When the sample is a solid, such measurements cannot be made by the Gouy method. The non-homogeneous-field method of Faraday has been described in various modifications, but in general these have not been devised for very small samples. The interference balance of Bathnagar and Mathur (*Phil. Mag.*, 1929, **8**, 1041) can be used with small samples, but is more elaborate than the present method and is not particularly easily adapted to measurements over a wide temperature range. Temperature control of the sample is easier when the measurements are made by a vertical-force method, as in Sucksmith's balance (*ibid.*, p. 158) and the present apparatus.

The balance now described consists essentially of a quartz torsion fibre microbalance by means of which the changing force on the sample under investigation may be measured as the magnet poles are moved vertically past the sample. Since the sample is small compared with the magnet, the accuracy of the method is not dependent on variations in the packing density. As, moreover, the measurements are all relative to a standard substance, extensive mapping of the field in the vertical direction is unnecessary and mapping in the horizontal plane is avoided by careful alignment of the sample with respect to the magnet pole-pieces, as described below.

The magnetic force as measured per mg. of sample is comparatively high in the present method. This force depends, of course, on the dimensions of the pole-gap as well as on the strength of the magnet; the former cannot be made too small, primarily because the apparatus for temperature control must be accommodated, and, secondly, because if the field gradient is too steep the alignment of the sample becomes too critical. With a magnet of maximum field strength about 2500 gauss, and a pole gap of 28 mm., the difference between the maximum and the minimum force on the sample is about 3×10^{-6} times its weight for a g.-susceptibility of 1×10^{-6}. Consequently the force on a 5-mg. sample of a moderately paramagnetic substance is of the order of 10—100 μg. and the necessary accuracy was made possible because the balance sensitivity was about 0·01 μg. The general layout of the balance is shown in Figs. 1 and 2.

Fig. 1.

Susceptibility balance, end view.



The Quartz Beam.—The beam is made of 200-μ. quartz rods and is supported at *O* by two 15-μ. horizontal torsion fibres, A, one of these is fixed, through the quartz tensioning bow *Q*, and the other is fused to 1-mm. quartz rod which in turn is cemented to the drive from a reduction gear, *B*. This gear,

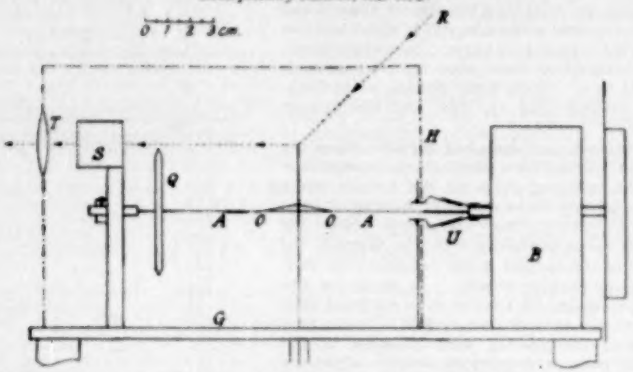
designed to eliminate back-lash, has a ratio of 20 : 1 and carries on its other axle a dial divided into 400 divisions to the full circle. Thus 8000 scale divisions are equivalent to one revolution of the end of the torsion fibre, which in turn corresponds to a change of weight of 60—70 μg. The exact calibration depends on the particular torsion fibre in use, of course, but the average fibre could be turned through 3½ revolutions either way from the relaxed position without breaking, corresponding to full scale deflexion of about 400 μg. The centre of gravity of the beam may be adjusted by bending the rod *F*.

The sample is contained in a fused quartz bucket *C*, 5—6 mm. long and of about 1-mm. internal diameter, having a fused quartz fibre handle and suspended from the beam by a 10-μ fibre *D*; it is counter-balanced by small pieces of platinum wire hanging from the other arm of the beam.

The Optical System.—A horizontal 5-μ index fibre *E* is held taut between two upright posts over the top of the beam. The balance is operated by bringing this fibre to a null position by rotation of the torsion head. This null point is determined by observing simultaneously the two ends of *E* by means of an optical system similar in principle to that described by Kirk, Craig, Gullberg, and Boyer (*Ind. Eng. Chem., Anal.*, 1947, **19**, 427). The images of the two ends are superimposed by a mirror-and-prism system *S*, of the type employed in microscope comparators, and brought to a focus by an achromatic convex lens *T* at the object position of a low-power microscope. A useful aid in determining the null point is to illuminate the ends of the index fibre with two different coloured lights *R*; when red and green are used there is a noticeable colour change at the exact superposition of the images. The total magnification of the optical system is about 80 ×.

FIG. 2.

Susceptibility balance, side view.



With relatively small loads, the angular motion of the beam caused by turning the torsion head is 0·11 minute of arc per scale division. After magnification, the relative motion in the eye-piece appears to be about 0·15 mm. per scale division; this figure is reduced by perhaps 50% for the largest loads used. Ideally the angular motion of the beam should be sufficient, therefore, to permit weighings to about 2 scale divisions or $1{\cdot}6 \times 10^{-6}$ g. This is actually found to be the reproducibility of any one setting, but other, more important errors exist, as will be shown below.

The Case.—The balance, and the optical system, with the exception of the viewing microscope, are attached to a thick brass plate *G* enclosed in a brass box, which in turn is surrounded by a wooden case *H*. Glass windows are inserted in the top of the boxes for the illumination of the index fibre. As far as possible, the inner box is made air-tight, leakage around the torsion head being prevented by the ground joint *U*. The assembly stands on four substantial brass legs attached to a base plate which also supports the screw device *J* for raising and lowering the magnet in the space between the balance legs. Vibrations of the beam are rapidly damped by air resistance, and the balance can be operated on an ordinary laboratory bench; a concrete pillar is not necessary.

The Magnet.—The magnet *I* is of a permanent magnetron type with a field strength at the mid-point between the poles of 2500 gauss. It has parallel circular pole faces *P*, 31 mm. in diameter and 29 mm. apart. For normal operation the maximum vertical travel of the magnet needs to be about 6 cm.

Temperature Control.—Control of the sample temperature is obtained by a set of interchangeable jackets small enough to fit between the magnet pole faces. All the jackets have an inlet *M* for dry nitrogen, which is used to surround the samples for all measurements.

The sample can be maintained at 20° by a water jacket *K* containing water circulated from a thermostat. A tube just wide enough to fit round the freely suspended sample and immersed in a small Dewar flask is used for liquid oxygen and solid carbon dioxide. A thermocouple *L* is incorporated in the tubes just below the sample. For temperatures up to 300° an electrically heated oven is used. This is of glass, wrapped in copper foil, with a non-inductive winding outside the foil and insulated from it by asbestos paper. The winding is tapped at the centre so that the upper and the lower half of the furnace

can be controlled independently. Heat insulation on the outside is provided by more asbestos, and the furnace has two thermocouple inlets about 1 cm. above and below the sample respectively. Each jacket is ground flat at the top, and a seal with the case is effected by the rubber gasket *N*.

Operation of the Balance.—When the sample is on the balance, the magnet is moved vertically past it in steps of 1 mm. At each step the beam is restored to its null position, and the torsion head reading is observed. The magnetic force so measured is given by :

$$F = m\chi H \, dH/dx$$

for a sample of mass m and susceptibility χ in a field of strength H, where x measures the position of the sample relative to the magnet in a vertical direction. A plot of F, measured in balance scale divisions, against sample position shows a maximum and a minimum (Fig. 3).

FIG. 3.

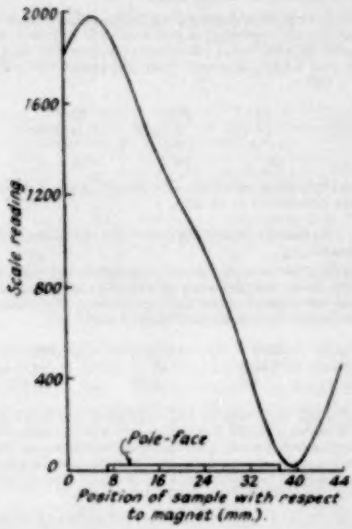
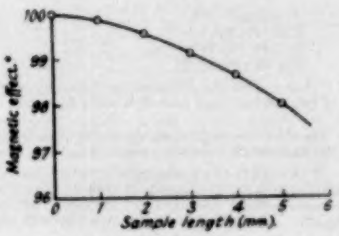


FIG. 4.



* Magnetic effect on the sample compared with zero length (%).

The magnetic effect on the empty sample-container is measured first and then the sample is weighed on an ordinary microbalance. The weight of the sample and container is counterbalanced on the susceptibility apparatus by platinum wire tares, and only the varying magnetic forces are balanced by the torsion head. At the same magnet positions, the scale reading obtained for the empty container are subtracted from those of the sample plus container to give the effect on the sample alone. The exact values of the maximum and minimum on the sample curve are then obtained graphically and the distance between them, in scale divisions, is used to calculate the susceptibility. Since the measurements are made relative to a standard substance, the g.-susceptibility (χ_1) of an unknown is given by :

$$\chi_1 = \frac{(s_1 - s_p)(m_2 - m_p)}{(m_1 - m_p)(s_2 - s_p)} \chi_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where, χ_2 = g.-susceptibility of the standard, s_1, s_2, s_p = the magnet forces on respectively (i) the sample plus container, (ii) the standard plus container, and (iii) the empty container, m_1, m_2, m_p = the weights respectively of (i), (ii), and (iii).

Since the method depends on comparing the magnetic effects on a sample and on the standard when placed in the same magnetic field, it is pertinent to enquire how reproducible the position of the sample container must be from one measurement to the next.

An experiment with a small sample of ferrous ammonium sulphate showed that the magnetic force differed by less than 0·9% over all horizontal positions within 1 mm. of the centre of the field. By moving the magnet the sample is always aligned to within 0·1 mm. of the centre (measured by a travelling microscope) so that errors from this source are negligible.

The alignment of the sample in the vertical direction introduces two possible errors : (i) the length of the sample may not be very small relative to the distance over which $H \, dH/dx$ is sufficiently close to its maximum value, and (ii) the sag of the torsion fibre under different loads may mean that readings on the sample plus container and on the container alone are not made at precisely the same place.

(i) The correction for the finite length of the sample was found by determining the curve of magnetic force against position for a small piece of platinum foil (1·5 × 1·5 × 0·1 mm.) hung with its plane horizontal so that its length was negligible. By graphical integration of the curve for various distances round the maximum, the relative force on samples of different lengths was calculated and hence a correction factor for the length. The correction curve is shown in Fig. 4.

(ii) The sag of the torsion fibre increases slightly when the empty sample container is loaded. Direct measurement showed that this introduced no significant error (<2 scale divisions) into the determination of the magnetic force on the sample alone.

Accuracy of Measurements.—Examination of the accuracy of the measurements yielded the following results.

(1) With the magnet removed, the torsion head was repeatedly turned away from the null position and brought back again. The root mean square deviation (σ) of the readings of the null position was about 1 scale division under a 1-mg. load, and 2·0 scale divisions for a 20-mg. load.

(2) A piece of 50 S.W.G. platinum wire (86·9 μg.) was weighed repeatedly on the balance. This was done at all parts of the torsion head scale by changing the counterweights and also with different total loads on the balance. No detectable difference in sensitivity was found for various parts of the scale up to 3½ fibre revolutions from the relaxed position. It was found, however, that the sensitivity varied slightly with the load as shown below.

Total load, mg.	1·0	20·7	31·3
Relative sensitivity	1	0·9987	0·9982
σ, scale divisions *	3·0	9·7	9·2
No. of weighings	10	10	10

* σ = root mean square deviation in weight found for platinum wire; this weight is the difference of two dial settings and 8000 scale divisions = 1 fibre revolution = 70 μg.

The σ for the mean relative sensitivities is 0·0003. The change in sensitivity for the operating region of the balance (20—30 mg.) was so small that it was ignored.

(3) A sample of a paramagnetic substance (uranium dioxide) was placed on the balance and, with the magnet replaced, the maximum and minimum forces due to the magnet were measured in the usual way. The same sample was measured ten times, and over different regions of the scale by altering the counterweights. The load in each case was about 25 mg.; the results for 3 different samples were:

Difference in scale divisions	2231	9570	20,900
σ	15½	25	21
σ/difference, %	0·7	0·26	0·10

It was found that merely taking the sample on and off the balance and adjusting the magnet if necessary, but not altering the counterweights, gave a much smaller deviation. It will be seen that altering the counterweights causes a sharp rise in the experimental error, the reason for which is not clear. Part of the extra rise with magnetic measurements is because the maxima and minima are found by graphical interpolation from 5 or 6 readings at successive magnet positions, and it cannot be claimed that these interpolations are better than ±5 scale divisions for the larger values of the differences.

As regards the total error of the measurements, equation (1) above leads to the following expression, approximately, for σ_χ, the r.m.s. error in χ_1:

$$\left[\frac{\sigma_\chi}{\chi_1}\right]^2 = \frac{1}{n_1}\frac{(\sigma_{S_1}^2 + \sigma_{S_2}^2)}{(S_1 - S_2)^2} + \frac{1}{n_2}\cdot\frac{(\sigma_{S_2}^2 + \sigma_{S_2}^2)}{(S_1 - S_2)^2} + \frac{1}{n_1}\frac{(\sigma_{m_1}^2 + \sigma_{m_2}^2)}{(m_1 - m_2)^2} + \frac{1}{n_2}\frac{(\sigma_{m_1}^2 + \sigma_{m_2}^2)}{(m_1 - m_2)^2} \quad . \quad \text{(ii)}$$

where the subscripts to the various σ show the quantities to which they refer, and n_1 and n_2 are respectively the number of measurements on the unknown and on the calibrating substance. The errors in m_1, m_2 and m_p depend on the microbalance on which these weighings are made; a good commercial microbalance should have mean weighing errors not above 2—3 μg. in a sample weight of *ca.* 5 mg. and a weight of standard substance of 2—3 mg. Thus even if $n_1 = n_2 = 1$, the weighing errors are only 0·15%, *i.e.*, the σ_m parts of (ii) above are about $2·5 \times 10^{-6}$. In most cases the weighing error should be less than the errors in magnetic measurements. σ_{S_2} is about 15 as S_2 was about −2500 (the container of course is diamagnetic), and σ_1 and σ_2 are between 20 and 25 for reasonable sizes of samples. In the case of the very paramagnetic ferrous ammonium sulphate $S_1 - S_2$ was about 10,000 scale divisions per mg., and for a 2·5-mg. sample the second term on the right hand side of (ii) becomes $1 \times 10^{-6}/n_2$. The first term on the right hand side of (ii) is in general the largest: if 10 mg. of a compound of $\chi = 1 \times 10^{-6}$ are used, $S_1 - S_2 = 3750$ approximately, so that S_1 is about 1250. If we put $\sigma_{S_1} = \sigma_{S_2} = 15$, this term in (ii) equals 32×10^{-6}. With these values, and if $n_1 = n_2 = 1$, $\sigma_\chi/\chi = 0·6\%$; but of course, a number of calibration runs was made and n_2 does not need to be large for σ_χ/χ to be considerably below 0·5%. The accuracy for compounds of high susceptibility is considerably better, of course. These estimates naturally include only the random errors of the instrument, though the method is sufficiently simple to make it improbable that other large errors are involved and the estimates agree quite well with experiment. It should however be noted that χ_2, the susceptibility of the standard substance, is assumed as known. The chief dangers are ferro-magnetic impurities, and if only one magnet is used these are not detected by the magnetic measurements themselves; they have to be avoided by careful preparation and analysis of both the standard substance and the unknown. With two permanent magnets of different strengths or with an electromagnet it is possible to be sure that χ is independent of H.

In the calibration of the present instrument a pure grade of ferrous ammonium sulphate was used as a standard. Analysis gave no measurable deviation from the calculated amount of ferrous ion present. In order to prevent loss of water of crystallisation measurements were made in an atmosphere of nitrogen which had been passed over saturated sodium bromide solution.

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449. *Magnetochemistry of the Heaviest Elements. Part II. The Oxides of Uranium.*

By J. K. DAWSON and M. W. LISTER.*

Measurements have been made of the magnetic susceptibilities of UO_2 and intermediate oxides up to U_3O_8 over the approximate temperature range 90—570° K., and the results have been correlated with tensimetric and *X*-ray studies of this system. Oxides between UO_2 and $UO_{2.4}$ follow the Weiss–Curie law with high values of Δ, and the susceptibilities are consistent with the view that these oxides contain quadri- and sexi-valent, but no quinquevalent, uranium. The magnetic moment of UO_2 has a value corresponding to a $5f^2$ (or $5f^1$, $6d^1$) rather than a $6d^2$ electronic configuration.

Above $UO_{2.4}$ there is a two-phase region; reproducible oxides in this middle region are difficult to obtain and give susceptibilities which do not follow the Weiss–Curie law. The exact upper limit of the two-phase region was not defined. It is necessary to express the susceptibility–temperature behaviour of U_3O_8 in the form $(\chi - \delta)(T + \Delta) = C$. U_3O_8 has a magnetic moment much below that predicted for $UO_2,2UO_3$; the moment agrees more nearly with that of U_2O_3,UO_3, but this requires a rather low value for quinquevalent uranium.

The susceptibility of UO has been measured in UO–UO_2 mixtures.

A STUDY of the oxides between UO_2 and $UO_{2.9}$ by means of *X*-ray-diffraction measurements and observation of the kinetics of oxidation has been reported recently by Anderson and Alberman (*J.*, 1949, S 303). They find that UO_2, which has a fluorite-type structure, will react with oxygen at moderate temperatures up to a composition about $UO_{2.4}$ while retaining the same structure and with very little change in cell dimensions. Further oxidation at temperatures below 230° C. leads to oxides with a composition up to $UO_{2.5}$; these oxides have a tetragonal structure with a c/a ratio quite close to unity. The low-temperature oxidation stops at $UO_{2.6}$, but, when heated, the latter substance disproportionates into $UO_{2.4}$ and a U_3O_8 phase. The U_3O_8 is also stable over a range of compositions, extending downwards as far as U_3O_8 according to Rundle, Baenziger, and Wilson (*J. Amer. Chem. Soc.*, 1948, **70**, 99). A two-phase region probably extends from $UO_{2.9}$ to U_3O_8.

It was thought that magnetic measurements would be of use in interpreting the changes involved in these oxidations. In particular, it should be possible to deduce whether quadrivalent uranium is replaced by quinque- or sexi-valent uranium as the oxidation proceeds. In addition, the susceptibility–temperature relations should be of interest, as this is a good example of the progressive dilution of a paramagnetic ion in a regular and more-or-less constant crystal environment. Finally, the magnetic measurements might also help to fix the boundaries of stability of the various phases in the uranium oxide system; this is difficult with *X*-ray measurements alone since subsidiary phases existing in a sample in proportions less than about 5% can remain undetected.

EXPERIMENTAL.

The magnetic measurements were all made on the susceptibility balance described in Part I (preceding paper), the sample size being in the region of 2—10 mg. The sources of experimental error are discussed in that paper; the root mean square errors of the susceptibilities given below are estimated to be between 0·5 and 1·0%.

The UO_2 was a pure commercial grade and there are two main possible sources of error from impurities: traces of ferro-magnetic impurities and the products of partial oxidation. Since the susceptibility measurements were made at one field strength they did not in themselves detect ferro-magnetic impurities and it was necessary to be sure of their absence by other means. Spectroscopic examinations of the UO_2 gave a content of Fe, Mn, Ni, and Co, which could have contributed about 1% to the observed susceptibility, assuming that they were present in a ferro-magnetic form. However, the consistency of the

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change in susceptibility as the sample was oxidised and the agreement of the susceptibility of the U_3O_8 eventually formed with that prepared from other sources make it improbable that these impurities were contributing more than the experimental error from other causes (*ca.* 0·5%). For a check against the products of partial oxidation a sample was weighed on a commercial micro-balance and then oxidised in air to U_3O_8; the increase in weight was measured on the quartz torsion fibre microbalance. 8·506 Mg. of UO_2 gave an increase in weight of 335·25 μg., or 3·9% (calc. for $UO_2 \longrightarrow U_3O_8$, 3·9%). The composition of the intermediate oxides was calculated from the take-up of oxygen during their oxidation from UO_2. These intermediate oxides were obtained from Anderson and Alberman, and were those used in their *X*-ray investigations (*loc. cit.*).

Measurements on UO–UO_2 *Mixtures.*—The mixtures were made as follows. Uranium metal, obtained in a finely divided state by heating UH_3, was allowed to react with an amount of oxygen insufficient to convert it into UO_2 and the product was heated to about 2000° in a vacuum furnace. Part of the uranium sintered to a bead of metal which effectively removed it from the reaction zone, but part formed UO according to the reaction, $U + UO_2 \longrightarrow 2UO$. The product was passed through a 200-mesh sieve and washed with dilute hydrochloric acid which dissolved the remaining metal but not the UO and UO_2. After washing and drying of the product, no metallic beads could be observed in the oxide mixture under a microscope. The composition of the samples used for susceptibility measurements was determined after the latter by measuring the increase in weight on oxidation in air to U_3O_8. The magnetic susceptibility of the U_3O_8 so formed was measured also and was identical with that of the U_3O_8 produced by oxidation of the pure UO_2: this served as a check, both on the completeness of the oxidation and on the purity of the sample.

TABLE I.

Sample A. Mean composition $UO_{1\cdot 995}$.

Temp., °K.	197·5	293	335	399	453·5
$10^6\chi_m$	10·36	8·45	7·79	7·01	6·41
$10^6\chi_{UO}$	7·23	6·41	5·73	5·31	4·69

Sample B. Mean composition $UO_{1\cdot 994}$.

Temp., ° K.	197·5	293	332·5	398	453·5
$10^6\chi_m$	10·47	8·38	7·79	7·02	6·46
$10^6\chi_{UO}$	8·18	6·15	5·64	5·44	5·19

TABLE II.

UO_2: Temp., ° K.	90	197	293	375	423	476	525	563				
$10^6\chi$	14·77	10·90	8·74	7·55	7·00	6·57	6·04	5·75				
$UO_{2\cdot 06}$: Temp., ° K.	197	293	335	405·5	445							
$10^6\chi$	10·20	8·15	7·49	6·64	6·27							
$UO_{2\cdot 11}$: Temp., ° K.	90	197	293	335·5	397·5	449	497					
$10^6\chi$	13·98	9·79	7·73	7·10	6·33	5·83	5·45					
$UO_{2\cdot 13}$: Temp., ° K.	90	195	293	398·5	432	482·5	517	562·5				
$10^6\chi$	13·71	9·10	7·07	5·75	5·42	5·01	4·74	4·42				
$UO_{2\cdot 50}$: Temp., ° K.	293											
$10^6\chi$	6·95											
$UO_{2\cdot 72}$: Temp., ° K.	197·5	293	333	398	400	449						
$10^6\chi$	8·33	6·41	5·88	5·20	5·18	4·78						
$UO_{2\cdot 80}$: Temp., ° K.	90	198	276	293	336	349	372	399	399·5	432·5	493	
$10^6\chi$	11·52	7·90	6·32	6·02	5·49	5·35	5·11	4·85	4·84	4·42	4·13	
$UO_{2\cdot 960}$: Temp., °K.	90	197	198	293	332·5	398	449·5	500·5	550			
$10^6\chi$	9·31	5·87	5·84	4·49	4·12	3·63	3·32	3·08	2·90			
$UO_{2\cdot 02}$: Temp., ° K.	90	197	293	333·5	398	447·5	482·5	498·5	514·5			
$10^6\chi$	8·76	5·54	4·31	3·94	3·50	3·23	3·07	2·98	2·94			
$UO_{2\cdot 03}$: Temp., ° K.	90	195	293	374	425	449	473·5	537	569·5			
$10^6\chi$	5·90	3·87	2·99	2·62	2·31	2·22	2·16	1·97	1·93			
$UO_{2\cdot 10}$: Temp., ° K.	202	276·5	293	312	333	354	372·5	398·5	423·5	442·5		
$10^6\chi$	2·89	2·75	2·62	2·53	2·43	2·34	2·27	2·165	2·08	2·02		
$UO_{2\cdot 07}$: Temp., ° K.	90	197	293	335·5	398	447	497	554				
$10^6\chi$	3·28	2·09	1·64	1·51	1·38	1·29	1·21	1·15				

From the susceptibility of the samples the susceptibility of UO (see Table I) was calculated by assuming that the samples were simple mixtures of UO and UO_2 obeying Wiedermann's law, *i.e.*, by subtracting the susceptibility of UO_2 at the corresponding temperatures interpolated from the results on pure UO_2. Thus in the first sample the mean composition was $UO_{1\cdot 995}$ so that 1 g. of the mixture contained 0·853 g. of UO_2 and 0·147 g. of UO. If χ_m is the g.-susceptibility of the mixture,

$$\chi_m = 0{\cdot}853\chi_{UO_2} + 0{\cdot}147\chi_{UO}$$

$$\text{or } \chi_{UO} = 6{\cdot}80\chi_m - 5{\cdot}80\chi_{UO_2} \text{ in sample } A$$

$$\text{and } \chi_{UO} = 6{\cdot}33\chi_m - 5{\cdot}33\chi_{UO_2} \text{ in sample } B$$

The calculated susceptibilities for UO are subject to relatively large errors; any error in χ_m is magnified 6—7 times in χ_{UO}. An error of 0·01 in the U : O ratio gives an error of about 0·45 in this region in the constants of the equations used to calculate χ_{UO}, and hence an error of about 0·15 in χ_{UO}. Consequently the accuracy of the results for UO is not better than about $\pm 5\%$.

The results were corrected by 43×10^{-6} per mole for the diamagnetism of the oxygen and also of the uranium atoms themselves (calculated according to Angus, *Proc. Roy. Soc.*, 1932, *A*, **136**, 569). Although the points in a plot of $1/\chi$ against T were rather widely scattered, the results seemed to follow the Weiss–Curie law and a least squares evaluation of the constants gave $\mu = 2{\cdot}76$, $\Delta = 286°$. If all the four electrons of the U(II) ions are in the $5f$ shell with normal L–S coupling, the moment may be calculated as 2·68 Bohr magnetons. The closeness of this to the measured values is probably coincidental, however, in view of the high magnetic concentration of the ions and the high value of the molecular field constant. Normal L–S coupling and a $6d^2$ configuration leads to a calculated effective moment of 0·00, while the spin-only value is 4·90. The measured value lies between these extremes and might be interpreted as incomplete orbital quenching of the $6d$ electrons, but more accurate and more numerous results are needed before any detailed discussion is possible.

Measurements on Oxides between UO_2 *and* U_4O_9.—Table II gives the g.-susceptibilities measured, no diamagnetic correction having been applied.

At the end of each series, the sample was returned to 293° K. and that measurement was repeated so as to detect any oxidation. In the cases where the measurements are not given to the highest temperatures, this usually means that oxidation by residual oxygen in the balance case set in. This could be detected by steady drifting of the balance owing to the increase in weight, and when the 293° K. reading was repeated the susceptibility was lower than that of the original sample.

Discussion.

The Magnetic Moment of UO_2.—From the above results, the magnetic moment of UO_2 is found to be 3·11 Bohr magnetons and $\Delta = 219{\cdot}5°$ K. by the least squares method. After correction for the diamagnetism of the oxygen and uranium atoms, the respective values become $\mu = 3{\cdot}20$, $\Delta = 233°$ for the U(IV) ion.

Apart from the observation that the susceptibility–temperature relation follows the Curie–Weiss law, these results are not in close agreement with those published previously by other authors. Thus Wedekind and Horst (Internat. Crit. Tables, Vol. VI, p. 359) give $\chi_{1/r} = 7{\cdot}5 \times 10^{-4}$, and Sucksmith (*Phil. Mag.*, 1935, **14**, 1115) obtained results which give $\Delta = 310°$, $\mu = 4{\cdot}36$ Bohr magnetons. Haraldesen and Bakken (*Naturwiss.*, 1940, **28**, 127) find $\Delta = 180°$, $\mu = 2{\cdot}92$.

For two unpaired electrons, as is the case in the U(IV) ion, the various electronic possibilities and their corresponding theoretical magnetic moments are given in Table III.

Table III.

		Moment (Bohr magnetons).		
Configuration.	Ground state.	L–S coupling.	Spin only.	jj coupling.
$5f^2$	$^3H_4$	3·58	2·83	3·84
$6d^2$	$^3F_2$	1·63	2·83	1·96
$5f^16d^1$	$^3H_4$	3·58	2·83	3·74

In view of the high magnetic concentration in the oxide lattice one would not expect to find that experimental values of the magnetic moment of the U(IV) ion would agree with either of the two possible extreme theoretical values of 3·58 and 1·63 based on the assumption of no interaction between the ions. It is also probable that the experimental moment would not correspond exactly to the " spin only " values of 2·83 Bohr magnetons since the lattice symmetry of UO_2 is cubic, and Bethe (*Z. Physik*, 1930, **60**, 218) has shown theoretically that systems of cubic symmetry will not remove all the degeneracy. The actually determined value of 3·20 Bohr magnetons indicates that the electrons are in $5f$ (or possibly $5f/6d$) states and that partial quenching of their orbital contributions occurs, the screening effect of the outer electrons being much less effective than in rare-earth ions. It is interesting to compare these results with those of Elliot (*Physical Rev.*, 1949, **76**, 431) on UF_4. Fluorides are generally considered to be similar to oxides as regards magnetic concentration, and the moment of UF_4 is 3·30—also higher than any value to be expected from a $6d^2$ configuration.

The Region UO_2 *to* $UO_{2\cdot3}$.—UO_2 and the intermediate oxides up to $UO_{2\cdot3}$ obey the Curie–Weiss law with reasonable accuracy over the temperature range studied. The values of Δ are all positive and comparatively large. The susceptibilities were corrected for diamagnetism (method of Angus, *loc. cit.*), the values used being $-11{\cdot}25 \times 10^{-6}$ per g.-ion of O^{--} and $-31{\cdot}5 \times 10^{-6}$ per g. of uranium. These corrections are comparatively small and do not disturb

the adherence to the Curie–Weiss law. They do alter the values of Δ and C somewhat, as may be seen in Table IV which gives the values of Δ and C in the equation $\chi(T + \Delta) = C$, calculated on a g. basis. It is usual to calculate from susceptibility data an effective moment for the paramagnetic atoms or ions by the equations

$$\chi_m = N\mu_{eff}^2\beta^2/[3K(T + \Delta)]$$

$$\mu_{eff.} = 2{\cdot}83\sqrt{\chi_m(T + \Delta)}$$

Except for UO_4 itself, the difficulty is to know whether to calculate a mean magnetic moment (assuming all the uranium atoms to be equivalent) or to make assumptions as to the different species of uranium ions present. In the latter case three possibilities arise : (i) U(IV) and U(VI), (ii) U(IV) and U(V), (iii) U(IV), U(V), and U(VI).

Ignoring for the moment the question of resonance, we may assume, as a first approximation at least, that the susceptibilities obey Wiedermann's law of addition. U(VI), whether as UO_2^{++} or U^{6+}, may be taken as diamagnetic and its contribution to the susceptibility disregarded for the present purpose. (This ion is sometimes reported as having a temperature-independent paramagnetism but this is still relatively quite small.) Consequently, under assumption (i) above, χ should be approximately constant in the various compounds of composition UO_{2+x} for quantities of material containing 1 g.-mol. of U(IV), or $1/(1 - x)$ g.-mol. of U atom. The calculation of susceptibilities per g.-mol. of U(IV) from the results in Table II leads to the values quoted in Table V. The points obtained by plotting $1/\chi$ against T lie very close to a straight line for each compound and lead to the following effective moments defined by $\mu_{eff.} = 2{\cdot}83\sqrt{\chi U(IV) \cdot (T + \Delta)}$

$(2 + x)$	2·00	2·06	2·11	2·18	2·25	2·30
$\mu_{eff.}$	3·20	3·13	3·09	3·01	2·97	2·94

Thus, while at room temperature there is reasonable constancy for $\chi U(IV)$ (italicised values in Table V), sufficient to suggest that (i) is the right interpretation of the uranium valency states

TABLE IV.

$(2 + x)$	2·00	2·06	2·11	2·18	2·25	2·30
Δ_1	219·5	200·5	181	158	145·5	131
Δ_2	233·5	212·5	198	170	160·5	144
C	1·282	1·221	1·193	1·129	1·106	1·083

$(2 + x)$ is the oxygen constituent of UO_{2+x}. Δ_1 is uncorrected for diamagnetism. Δ_2 is corrected for the diamagnetism of the oxygen and the uranium.

TABLE V.

	Temp., °K.	χ per U(IV), $\times 10^6$.	χ per U(IV) corrected for diamagnetism, $\times 10^6$.		Temp., °K.	χ per U(IV), $\times 10^6$.	χ per U(IV) corrected for diamagnetism, $\times 10^6$.
UO_2	90	3989	4043	$UO_{2\cdot19}$ ...	90	4551	4619
	197	2944	2998		195	3030	3098
	293	2362	*2416*		293	2355	*2423*
	375	2038	2092		398·5	1914	1982
	423	1891	1945		432	1804	1872
	476	1774	1828		482·5	1668	1736
	525	1632	1686		517	1579	1647
	563	1553	1607		562·5	1470	1538
$UO_{2\cdot08}$	197	2942	3000	$UO_{2\cdot25}$ ...	197·5	3043	3119
	293	2350	*2408*		293	3241	*2417*
	335	2161	2219		333	2150	2226
	405·5	1914	1972		398	1902	1978
	445	1809	1867		400	1895	1971
					449	1748	1824
$UO_{2\cdot11}$	90	4289	4332				
	197	2985	3048	$UO_{2\cdot30}$	90	4543	4625
	293	2357	*2420*		198	3117	3199
	333·5	2164	2227		293	2376	*2458*
	397·5	1930	1993		336	2166	2248
	449	1777	1840		349	2109	2191
	497	1660	1723		372	2013	2095
					399·5	1908	1990
					452·5	1744	1826
					493	1630	1712

present, this is to some extent a combination of two opposing variations in $\mu_{eff.}$ and Δ. This point will be discussed in more detail later.

Because of the lack of experimental data on the magnetic moment of U(V) and the uncertainty regarding the amount of coupling, it is difficult to test assumption (ii) quantitatively. Qualitatively, however, it appears that assumption (i) is in better agreement with the facts.

In connection with assumption (iii), the equilibrium

$$U(IV) + U(VI) \rightleftharpoons 2U(V) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (i)$$

would involve only an electron transfer. Since UO_2 is a semi-conductor, an equilibrium distribution of electrons between the uranium atoms in the several valency states must be attained; however the proportion of U(V) appears to be too small to contribute substantially to the magnetic measurements. The reason may be that U(VI) is invariably stabilised by covalency and it seems probable that the extra oxygen in these intermediate oxides would be linked by predominantly covalent bonds.

The Decrease in $\mu_{eff.}$ per U(IV) *with Increasing Oxygen Content.*—As shown above, while the composition moves from UO_2 to $UO_{2\cdot3}$, the effective moment of U(IV) decreases from 3·20 to 2·94 Bohr magnetons.

UO_2 has the fluorite structure, and extra oxygen is almost certainly accommodated in interstitial $(\frac{1}{2},0,0)$ positions. For a number of reasons, *e.g.*, the general chemistry of U(VI) compounds, the polarising effect of U^{6+} ion, the dimensional constancy of the cubic UO_{2+x} phase, it can be argued that the interstitial oxygen is so bound as to approximate to UO_2^{2+} (or UO^{4+}) groups in the structure. The dissymmetry so produced in the electric field of the crystal lattice would increase the quenching of the orbital angular momentum. This could account for the reduction in effective moment of the U(IV) ions, though the magnitude of the effect cannot be exactly computed.

Systems in which the contribution of the orbital momentum is suppressed usually obey the Curie–Weiss law $\chi(T + \Delta) = C$ with appreciable values of Δ. Table IV shows that the Δ values in the combounds under discussion are all large and positive. The Weiss theory of the internal molecular field can be shown to lead to a regularity in the behaviour of Δ similar to that found experimentally. According to this theory the atoms are assumed to be subject, in addition to the externally applied field H, to an internal field proportional to the mean resultant moment of an atom as a result of the orienting effect of H. If the atom has total angular momentum J, the resultant expression for χ_m is

$$\chi_m = \frac{NJ(J+1)g^2\mu_B^2}{3k} \times \frac{1}{T - \frac{\nu J(J+1)g^2\mu_B^2 n}{3k}} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (ii)$$

where N = Avogadro's number, g = Lande's splitting factor, μ_B = the moment of the ion in Bohr magnetons, k = gas constant, ν = a constant, characteristic of the internal field, and n = the number of atoms per c.c.

The total internal field is taken to be $F = H + n\overline{m}$ where $\overline{m}$ is the average moment. Whence

$$\Delta = -\nu C(1 - x)/V \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (iii)$$

where V = molar volume of 1 g. of U atoms, *i.e.*, $V/(1 - x)$ = molar volume of the U(IV) atoms in UO_{2+x}. The result (iii) is obtained by assuming that the crystals have a perfect cation lattice; for a perfect anion lattice the expression for Δ becomes

$$\Delta = \frac{-\nu C(1 - x)}{V(1 + 0{\cdot}5x)} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (iv)$$

since $V(1 + 0{\cdot}5x)/(1 - x)$ is now the molar volume of U(IV) atoms. It is evident that equations (iii) and the general form of (ii) are unaltered if only the spin moment is effective (J becomes S and $g = 2$). The applicability of (iii) or (iv) may be tested by examining the constancy of ν calculated from the data obtained. The *X*-ray data and the mode of preparation make it probable that (iii) should apply to these lower oxides (Anderson and Alberman, *loc. cit.*, from which source the cell dimensions were also obtained). The results for the compounds expressed as UO_{2+x} are:

$(2 + x)$	2·00	2·06	2·11	2·18	2·25	2·30
$-\nu$	4440	4510	4560	4480	4700	4590

In view of the experimental errors, these values of ν are reasonably constant: the negative sign arises from the fact that these compounds have an apparent negative Curie point. The constancy of ν shows that Δ arises from some (unspecified, as yet) interaction between the U(IV) ions and that this interaction makes them *less* liable to mutual alignment in the external field *H*. The interaction is proportional to the number of U(IV) ions per unit volume and presumably it must be of an exchange type in order to account for the large value of ν—magnetic interactions are much too small.

Note on an Annealed Sample, $UO_{2\cdot19}$.—According to Anderson and Alberman, oxides in the range $UO_{2\cdot3}$ to $UO_{2\cdot5}$ on prolonged heat treatment disproportionate into a pseudo-fluorite β-phase of composition close to $UO_{2\cdot3}$ and a higher phase, U_3O_8 or U_2O_5. A sample of composition $UO_{2\cdot19}$ was found to yield pure β-phase on annealing thus. Magnetic susceptibility measurements yielded a Δ value of 152·5° and $C = 1{\cdot}145$. According to equation (iii) above, this compound gives a ν of −4010, whilst ν from equation (iv) is −4390. The *X*-ray data suggest that annealed $UO_{2\cdot19}$ would have a perfect anion lattice and that equation (iv) should be applicable. It is interesting to note that this is confirmed by the closeness of the value of ν to those obtained for the unannealed oxides according to equation (iii).

The Region $UO_{2\cdot3}$ to $UO_{2\cdot67}$.—The oxides in the region $UO_{2\cdot3}$ to $UO_{2\cdot5}$, and possibly even further, are certainly mixtures. Furthermore, they are not necessarily mixtures of only the same two phases, since the lower phase may be $UO_{2\cdot3}$ or $UO_{2\cdot19}$ according to the degree of reorganisation of the crystal structure that has taken place before further oxidation. The upper phase is probably U_3O_8, but here again a range of composition is not impossible. Consequently the susceptibilities given in Table II for the oxides in this range have no very great significance, except to show that the range of stability of the UO_2-type phase certainly ends near to $UO_{2\cdot3}$, after which deviations from the previous regularities in susceptibility occur. These materials no longer obey the Curie–Weiss law, owing in part to their being mixtures of compounds with different Δ values, and also to the fact that U_3O_8 itself does not obey the same law.

The susceptibility–temperature relation of U_3O_8 very closely follows the form $(\chi - h)(T + \Delta) = C$. The actual values, expressed per g., are

$$(\chi - 0{\cdot}492 \times 10^{-6})(T + 51{\cdot}4) = 3{\cdot}94 \times 10^{-4} \quad \text{(v)}$$

The constant *h* is formally equivalent to a temperature-independent paramagnetism (as in the case of the platinum group compounds; Cabrera and Duperier, *Compt. rend.*, 1927, **185**, 414), of magnitude $133{\cdot}8 \times 10^{-6}$ per g.-atom of uranium, uncorrected for diamagnetism. A temperature-independent paramagnetism has been reported for U(VI) compounds by several investigators (Lawrence, *J. Amer. Chem. Soc.*, 1934, **54**, 776; Nicolau, *Compt. rend.*, 1937, **205**, 654; Tilk and Klemm, *Z. anorg. Chem.*, 1939, **240**, 355; Haraldsen and Bakken, *loc. cit.*). Consequently, the effect is quite to be expected if the U_3O_8 contains sexivalent uranium, although the magnitude is relatively large.

Using the equation

$$\mu = 2{\cdot}83\sqrt{(\chi - h)(T + \Delta)} \quad \text{(vi)}$$

the effective moment of U_3O_8 is 1·63 for a composition $UO_2{,}2UO_3$ and 1·15 for $UO_{2\cdot5}{,}\frac{1}{2}UO_3$. Both these values are lower than those calculated for two and one unpaired electrons respectively, although the value obtained for the U(V)–U(VI) combination agree most nearly. Consequently the structure of U_3O_8 seems to involve a U(V)–U(IV) mixture; this agrees with the conclusion drawn by Haraldsen and Bakken, although they report that the susceptibility follows the Curie–Weiss law.

If Δ and *C* are taken from equation (vi) for U_3O_8, then $\nu = \Delta V/C = 10{,}200$ when *C* is expressed per g.-atom of U(V). There is no particular reason why this should be the same as for UO_2, but it is obviously of the same order.

Note on the Uniformity of the Samples.—It is evident that if in a sample nominally taken as $UO_{2\cdot1}$ some of the grains are, in fact, $UO_{2\cdot3}$ and others are UO_2, this would not easily be detected in the magnetic measurements. Relatively heavy contamination by an oxide of different oxygen content would have the effect of producing a curve in the $1/\chi$–T line, but the only real guarantee of homogeneity comes from the kinetic studies of the oxidation by which the samples were prepared (Anderson and Alberman, *loc. cit.*). The grain size itself, as shown by the electron-microscope is very small, each grain containing about 10^7 unit cells. The activation energy of the oxidation is about 27 kcals. and the temperature of preparation about 200°.

The oxidation is found to be rapid and the oxygen must diffuse into the cells since the surface area is insufficient for only superficial oxidation. Consequently, with these small grains and

the relatively easy oxidation, it seems reasonable to suppose that there will have been time for the oxygen to become distributed during the annealing of the samples.

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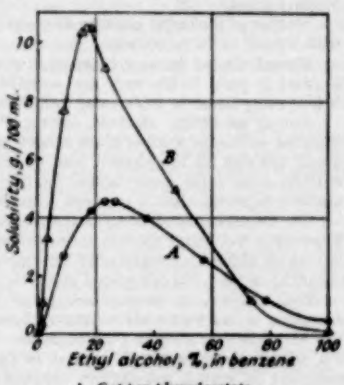
450. *Complexes of Copper Phenylacetate and Diphenylacetate with Alcohols.*

By MALCOLM CRAWFORD.

Copper phenylacetate and diphenylacetate are insoluble in benzene but dissolve readily when small amounts of other organic compounds, particularly alcohols, are added. This is attributed to the formation of complexes, many of which have in fact been isolated in the solid state and studied. Suggestions are made with regard to their constitution.

COPPER salts of many carboxylic acids are sufficiently soluble in benzene to impart to it a pale green colour. Only rarely is the solubility great enough to give a deep green solution. Copper phenylacetate, for example, is practically insoluble in benzene, but is slightly soluble in absolute ethyl alcohol (0·5 g. in 100 ml. at 25°). In the mixed solvents, however, the solubility is considerably greater, reaching a maximum of 4·5 g. in 100 ml. of 25% alcohol in benzene at 25°. The solubility curve is shown in Fig. 1.

FIG. 1.



A, *Copper phenylacetate.*
B, *Copper diphenylacetate.*

This behaviour indicates the likelihood of compound formation, yet when the solution in the mixed solvents is concentrated, the green needle crystals which separate on cooling consist of copper phenylacetate alone. The same effect is observed with other alcohols, such as *n*-propyl, *n*-butyl, and allyl, but in none of these cases have compounds been isolated.

Solubility data for copper diphenylacetate are also included in Fig. 1. In this case the effect is still more enhanced. The solubility in the pure solvents is negligible, but in 17% alcohol in benzene it reaches a maximum of 10·6 g. in 100 ml. at 25°. In addition to this, crystallisation from alcohol-rich mixtures gives light-green octahedral crystals containing two molecules of combined alcohol. From alcohol-poor mixtures dark-green needle crystals of copper diphenylacetate separate.

If the octahedral crystals are filtered off and stored in slightly damp condition they can be kept indefinitely, but on drying and exposure to the atmosphere they gradually lose alcohol over a period of a few weeks. When all the alcohol is gone the octahedral form remains intact but the colour has changed to a darker green. The solubility in benzene has also vanished. There would seem, therefore, to be little doubt that the enhanced solubility in the mixed solvents is due to compound formation.

Most other alcohols tested behave similarly to ethyl alcohol. Table 1 lists the compounds examined and the alcohols tested; some of these compounds were mentioned in a preliminary note (*Nature*, 1947, **160**, 19). It will be seen that several primary alcohols, *viz.*, *n*-propyl, allyl *n*-butyl, and *iso*butyl, form light-green octahedral crystalline compounds containing two molecules of alcohol similar to that formed by ethyl alcohol. All of them lose the combined alcohol within an hour at 100°, but at room temperature the allyl alcohol compound loses

weight more slowly than the others in spite of the similarity in volatility of allyl and the other alcohols. This compound is therefore more stable.

TABLE I.

Compounds of copper diphenylacetate with various alcohols.

Alcohol.	Compound. Crystalline form.	Colour.*	Stability.	Mols. of combined alcohol.
Methyl	Plates	Dark	Medium	1½—2 (variable)
Ethyl	Octahedra	Light	,,	2
n-Propyl	,,	,,	,,	2
Allyl	,,	,,	More stable	2
n-Butyl	,,	,,	Medium	2
*iso*Butyl	,,	,,	,,	2
n-Amyl	,,	,,	,,	1½
n-Hexyl	—	—	(No compound)	—
Benzyl	Needles	—	Very stable	2
n-Octadecyl	—	—	(No compound)	—
*iso*Propyl	—	—	,,	—
sec.-Butyl	Prisms	Dark	Very stable	Indefinite
*cyclo*Hexanol	Needles	—	,,	1
tert.-Butyl	Rhombs	Dark	,,	2
tert.-Amyl	Needles	—	,,	1
Triphenylcarbinol	—	—	(No compound)	—

* Colour only recorded where markedly light or dark green.

In the preparation of the n-amyl compound appropriate seeding of the supersaturated solution will produce either solvent-free needles or octahedra containing only 1½ molecules of the alcohol.

Neither of the larger primary alcohols tested, n-hexyl and n-octadecyl, was found to combine with copper diphenylacetate.

Benzyl alcohol forms a compound crystallising in needles. Its high stability may be due, at least in part, to the very low volatility of benzyl alcohol. The methyl alcohol compound is also exceptional in the crystal form, plates, and in its variable composition.

Among secondary alcohols, *iso*propyl alcohol could not be induced to form a compound, whereas *sec.*-butyl alcohol gives a dark green compound of indefinite composition, containing about 0·6 mol. of the alcohol, and of such stability that the alcohol could not be driven off entirely even after many hours' heating at 100°. *cyclo*Hexanol forms a 1 : 1 compound in needles, so stable that it required 7 hours at 100° to remove all the combined alcohol.

The two compounds with tertiary alcohols which have been examined are of high stability. That with *tert.*-butyl alcohol contains two molecules of the alcohol (rhombs), and that with *tert.*-amyl alcohol contains only one molecule of alcohol (needles). Neither loses weight on standing in air. No compound could be obtained from triphenylcarbinol.

The solubility in benzene and other hydrocarbon solvents ought to allow of easy determination of the molecular weight of these compounds. Difficulties arise, however, owing to the very low solubility in pure benzene. From the curves in Fig. 1 it can be seen that 1% or 2% of an alcohol must be present in the solvent before the solute reaches a concentration sufficient to give a satisfactory depression of the freezing point. The combined alcohol is insufficient to accomplish this. Nevertheless it is possible to prepare supersaturated solutions by dissolving the crystals in hot benzene, then cooling the solution and determining the depression before solute crystals separate.

TABLE II.

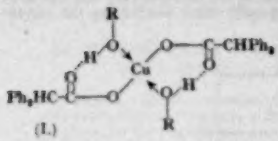
Molecular weight of copper diphenylacetate–diethanol complex in benzene at the freezing point.

Concn. of substance, % (w/w)	0·57	1·21	2·06
Δ	0·080°	0·159°	0·247°
M	358	386	426

Calc. for $C_{16}H_{22}O_4Cu,2C_2H_6O$: *M*, 378.

It will be seen from Table II that the ethyl alcohol compound is dissociated in benzene at its freezing point. It is probable but not certain that the compound contains one atom of copper in the molecule both in solution and in the solid state. The structure (I; R = Et) is suggested as probable.

The study of this series of complexes may help to throw light on certain aspects of solubility, particularly solvation and solubility in mixed solvents. The insolubility of copper diphenylacetate in benzene is not surprising. It is probably not so much due to the fact that it is a salt as that it is associated in the solid state to large stable molecules, either by ionic forces or by co-ordinate linkages, but certainly not by van der Waals forces alone.



(I.)

In the presence of alcohol, however, disaggregation to small molecules takes place because the monomeric molecule combines with the alcohol in preference to associating with itself. The resulting small molecules of the type (I) are soluble in benzene, as might be expected since the hydrophilic groups are screened by a hydrocarbon exterior and dissolve, therefore, like any hydrocarbon.

Work in progress (*Nature*, 1950, **165**, 726) shows that isolable complexes with alcohols are formed by the copper salts of several other organic acids. No complexes of copper phenylacetate can be isolated although from Fig. 1 they obviously exist in solution. It is likely that the particular stability of the copper diphenylacetate complexes is due to the shape of the molecule, which permits small molecules to attach themselves by weak linkages and fit into holes in the crystal lattice. This would be impossible where R in the alcohol ROH is too long or too bulky. The limit of length in this case would appear to be *n*-amyl alcohol, which is just too large to fill all the spaces available This does not necessarily apply in solution. Large alcohol molecules would still facilitate solution of copper diphenylacetate in benzene, but no stable crystals would be isolable, as indeed is found with *n*-hexyl and *n*-octadecyl alcohols. The very bulky alcohol, triphenylcarbinol, however, does not enhance the solubility of copper diphenylacetate in benzene, presumably because for steric reasons it cannot form a complex even in solution.

We have here cases of solvation where the actual number of solvating molecules can be assessed together with indications of the forces likely to be involved in the process, namely, hydrogen bonding and co-ordinate linkage aided by steric conditions allowing approach and assisting retention of the attached molecules even into the solid state.

Compounds of copper diphenylacetate with various ketones, aldehydes, esters, and amines have also been isolated, and will be described later.

Experimental.

Materials.—Copper diphenylacetate was prepared by mixing equivalent amounts of A.R. copper sulphate and sodium diphenylacetate, both in aqueous solution. The bulky green precipitate was well washed, dried at 100°, and crystallised from benzene–ethyl alcohol (4 : 1). After being washed, the needle crystals were dried at 100° (Found : Cu, 13·0, 13·0. Calc. for $C_{28}H_{22}O_4Cu$: Cu, 13·09%). Copper phenylacetate was prepared in similar fashion (Found : Cu, 19·0, 19·1. Calc. for $C_{16}H_{14}O_4Cu$: Cu, 19·05%).

The various liquid alcohols used were fractionally distilled, and a middle fraction selected. Triphenylcarbinol and *n*-octadecyl alcohol were purified by recrystallisation. The compounds for examination were obtained by heating copper diphenylacetate with the alcohol in question, benzene being added if necessary to effect solution. On cooling the solution the compound separated. In difficult cases most of the benzene had to be distilled off before cooling. The compounds were filtered off, washed with the alcohol and stoppered in tubes without drying. Occasionally alcohol-free copper diphenylacetate separated. The preparation was thereupon repeated more alcohol being used.

Methods.—The amount of combined alcohol was determined by loss of weight on heating at 100°. The initial dry weight of each sample was obtained by a process of " continuous weighing " (see Guichard, *Bull. Soc. chim.*, 1944, **11**, 63). A quantity of the substance is placed on a weighed watch glass and weighed at regular intervals. The weight is plotted against time. In the curve (Fig. 2) the rapid loss of adhering alcohol is represented by an initial steep fall, then there is a sharp break followed by gradual loss of combined alcohol. The point at which the two parts of the curve intersect gives fairly accurately the original dry weight of the compound. From the second part of the curve the rate of loss of combined alcohol can be used to gauge the stability.

All copper determinations were performed gravimetrically by means of salicylaldioxime. Volumetric methods were unreliable and required larger amounts of the substance.

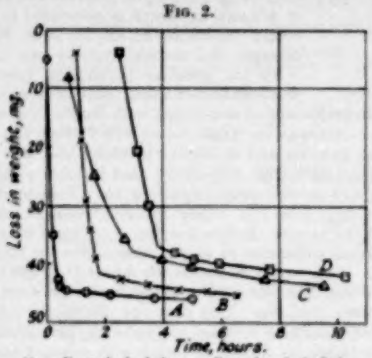
The solubility determinations were made by shaking excess of the substance with solvent in a closed vessel in a thermostat at 25° for one or two days or until two samples removed by pipette with filtering at one-day intervals agreed in dry weight after evaporation of the solvent. This method is sufficiently accurate for the purpose.

Copper Phenylacetate.—The determinations of solubility in alcohol–benzene mixtures are recorded in Fig. 1.

Complexes.—Copper phenylacetate was dissolved by warming separately with the following alcohols with the addition of benzene where necessary : *n*-propyl, *n*-butyl, *tert.*-butyl, allyl. On cooling, the crystals which separated were filtered off, washed with the appropriate alcohol, and subjected to continuous weighing to give the initial dry weight and then heated at 100°. The loss in weight on heating

was: *n*-propyl alcohol, 0·63; *n*-butyl alcohol, 0·19; *tert.*-butyl alcohol, 1·58; allyl alcohol, 3·76%. The losses are very small and show that there is no combined alcohol in the crystals, but that the allyl alcohol is more adherent than the others. There is no compound with ethyl alcohol, as the copper phenylacetate was obtained from that solvent as already described.

FIG. 2.



A, *Ethyl alcohol.* B, *n-Propyl alcohol.* C, *n-Amyl alcohol.* D, *n-Butyl alcohol.*

Copper Diphenylacetate.—The solubility determinations are recorded in Fig. 1.

Complexes.—Analytical data relating to the *complexes* isolated are given in Table III.

TABLE III.

Complexes of copper diphenylacetate with alcohols.

Complex.	Loss in wt. on heating, %. Found.	Reqd.	Copper, %. Found.	Reqd.	Copper, %, after heating. Found.	Reqd.
Diethanol	15·6, 16·1 15·9, 15·9	15·93	11·0, 10·8	11·0	13·0, 12·9	13·09
Di-*n*-propanol	20·5	19·83	—	—	—	—
Diprop-2-enol	19·5	19·30	—	—	—	—
Di-*n*-butanol	21·8, 21·7 20·5, 21·3	23·37	10·2, 10·4	10·03	12·9, 13·2	13·09
Di-2-methylpropanol	22·2, 23·9	23·37	—	—	—	—
Di-2-methyl-2-propanol	23·0	23·37	—	—	—	—
Sesqui-*n*-pentanol	21·3, 21·0	21·38	10·4, 10·4	10·29	13·2, 13·1	13·09
2-Methyl-2-butanol	15·3, 15·1	15·35	—	—	—	—
Dicyclohexanol	17·1	17·25	—	—	—	—
Bisphenylcarbinol	29·2	30·8	—	—	—	—
Methanol (sesqui-di):						
Preparation A	8·79, 8·75 0·86*	9·00 (1½)	1·8	11·91 (1½)	13·0	13·09
Preparation B	10·23, 10·24	11·65 (2)	11·7, 11·7	11·65 (2)	13·1, 13·1	13·09
2-Butanol			12·0	11·4		

* After standing for 8 months in contact with methanol.

The following alcohols failed to yield compounds.

iso-Propyl alcohol. On concentration of a solution of copper diphenylacetate in benzene–*iso*propyl alcohol, fine dark crystals separated (Found: Cu, 12·8; loss on heating, 1·67; Cu, after heating, 13·1. Calc. for $C_{32}H_{30}O_4Cu$: Cu, 13·09%). The crystals were therefore copper diphenylacetate with a small amount of adhering solvent.

n-Hexyl alcohol. A solution of copper diphenylacetate in a mixture of *n*-hexyl alcohol and benzene was distilled until most of the benzene had been removed. On standing for several days, green crystals of copper diphenylacetate separated (Found: Cu, 13·0, 13·0; loss on heating, 0·4, 0·4; Cu, after heating, 13·1, 13·1. Calc. for $C_{32}H_{30}O_4Cu$: Cu, 13·09%).

n-Octadecyl alcohol. Copper diphenylacetate dissolved in a heated solution of *n*-octadecyl alcohol in benzene. On cooling, the alcohol crystallised out together with a small amount of dark green needles having the characteristic appearance of copper diphenylacetate.

Triphenylcarbinol. A solution of triphenylcarbinol in benzene dissolved copper diphenylacetate only to the slightest extent.

WIGAN AND DISTRICT MINING AND TECHNICAL COLLEGE. [*Received, April 1st,* 1950.]

451. *The Kinetics of Halogen Addition to Unsaturated Compounds. Part XVIII. Iodine Addition.*

By P. W. Robertson (with the co-operation of J. B. Butchers, R. A. Durham, W. B. Healy, J. K. Heyes, J. K. Johannesson, and D. A. Tait).

This is a general revision of the kinetics of iodine addition, with a note on the equilibria in these reactions. The rate of iodine addition over the concentration range that can be measured is given by the expression

$$-d[I_2]/dt = k_1[A][I_2]^2 + k_2[A][I_2]^3$$

the first term being chiefly operative in solvents such as chlorobenzene, carbon tetrachloride, and carbon disulphide, and the second term in *iso*butyl ether, acetic acid, and nitrobenzene solutions. With certain aromatic compounds such as styrene and its derivatives iodine addition is accompanied by polymerisation.

An earlier investigation on the kinetics of iodine addition (Bythell and Robertson, *J.*, 1938, 173) established that these reactions, like the corresponding bromine and iodine chloride additions, showed third-order kinetics, with a small temperature coefficient in acetic acid and nitrobenzene solutions. Erroneous theoretical conclusions, however, were made from the measurements in carbon tetrachloride solution, chiefly as a result of confining the observations to a single compound, allyl alcohol, the behaviour of which is now found to be anomalous. In the meantime several communications on the kinetics of iodine addition have appeared. Bhattacharyya and Rao (*J. Indian Chem. Soc.*, 1941, **18**, 253), using 2-pentene and phenylacetylene as reactants, found third-order kinetics for iodine addition in acetic acid and ethyl alcohol solutions. Ghosh *et al.* (*ibid.*, p. 245) state that iodine addition in carbon tetrachloride, carbon disulphide, and benzene solutions proceeds by a fourth-order mechanism. These observers, following Groh and Szelestey (*Z. anorg. Chem.*, 1927, **162**, 333), who had previously investigated erucic acid in carbon tetrachloride and carbon disulphide and found fourth-order kinetics, employed an elaborate formula, derived from the integration of the expression, $-d[I_2]/dt = k_1[A][I_2]^2 - k_2[AII][I_2]^2$, and obtaining constant k_2 coefficients for β-amylene and pinene, concluded that the reaction proceeds, $A + I_2 \rightleftharpoons AII + 2I_2$.

We, on the other hand, have followed the simpler procedure of adjusting the concentrations with one reactant A in excess, to reduce the effect of the reverse reaction, and have evaluated the reaction order by measurements at different initial concentrations. To obtain the relative contributions of A and I_2 to the total reaction order, use was made of the formula :

$$t_2/t_1 = (c_1/c_2)^{n-1}\,(c'/c'')^{n'}$$

where t_1 and t_2 are the times of an equal fractional change of iodine addition, with concentrations c_1 and c_2 for I_2, and c' and c'' for A, n being the order for I_2 and n' for A. The proposed formula holds only for the initial stages of the reaction, to ~10% iodine addition, over which range, as is found experimentally, the % addition–time curves are approximately straight lines.

Employing this formula, we have established that in polar solvents, *e.g.*, acetic acid, *iso*butyl ether, chloroform, chlorobenzene, and nitrobenzene, the reaction order for the organic compound (A) is unity; in the non-polar solvents carbon tetrachloride and carbon disulphide, on the other hand, the value calculated for A is greater than one. This is not considered to be due to the participation of an addition compound, AI_2, in the reaction, because in such a compound the iodine would be unfavourably polarised for electrophilic attack; it is rather a solvent action in which the iodine molecule is polarised by the unsaturated compound, and is not found when the solvent itself is sufficiently polar. Another means by which the iodine molecule may be polarised is by a solid polar catalyst. With glass, such heterogeneous catalysis is slight, being not at all observable in polar solvents, and in carbon tetrachloride and carbon disulphide only at low iodine concentrations, as it is obscured at greater concentrations by the participation of high-order homogeneous reactions. The strongly polar barium sulphate is more effective than glass, and thus iodine addition is analogous to bromine addition, although the catalysis generally is weaker (*cf. J.*, 1945, 509).

As the result of a number of measurements, examples of which are given in the Experimental part, the rate of iodine addition may be shown by the general expression :

$$-d[I_2]/dt = k_1[A][I_2]^2 + k_2[A][I_2]^3$$

In chlorobenzene, and in carbon tetrachloride and carbon disulphide (violet solutions) when the concentration of the organic compound is not too great, with iodine concentration *ca.* N/50,

the first term chiefly is operative at 25°, whereas the second term is dominant in the solvents acetic acid, *iso*butyl ether, and nitrobenzene (brown solutions). The fourth-order reactions have a very small temperature coefficient, often not much greater than unity, whilst third-order addition is rather more sensitive to temperature. The reversible nature of iodine addition precludes the search for a second-order reaction at low concentrations. It is believed, however, that this mode of addition may not proceed, since on the addition of water to the solvent acetic acid (which for bromine addition causes a considerable increase in rate and a progressive change from third- to second-order kinetics) iodine addition is only slightly accelerated, and the reaction order remains unchanged.

It is apparent that, before it becomes reactive, the iodine molecule requires to be polarised, if not by a solid polar catalyst or a polar solvent, at least by another molecule of iodine, but it is not necessary to assume, as was done by Groh and Szelestey (*loc. cit.*), that in the fourth-order reactions iodine reacts as I_4 molecules. Groh and Tacaacs (*Z. physikal. Chem.*, 1930, **149**, 195) have shown that iodine does not obey Beer's law in carbon tetrachloride and carbon disulphide solutions, but this could also be explained as due to association to I_4 molecules. On this assumption two alternative schemes are available for fourth-order kinetics :

(*a*) $A + I_4 \rightleftharpoons AI_4$; $AI_4 + I_2 \rightleftharpoons AII + 2I_2$

(*b*) $A + I_4 \rightleftharpoons AI_2 + I_2$; $AI_2 + I_2 \rightleftharpoons AII + I_2$

According to each of these the final reaction is the relatively slow rate-determining stage, but whereas (*i.e.*, during the initial part of the reaction) in (*a*) stationary concentrations are maintained, in (*b*) the intermediate, AI_2, accumulates as the reaction proceeds. Iodine addition in showing mixed third- and fourth-order kinetics is thus similar to bromine addition and substitution, which reactions have been discussed in previous communications (*J.*, 1947, **633**; 1948, **101**).

The reason why the reaction order is less in the brown solutions, in which there is compound formation, is due to the fact that the equilibrium, $I_4 \rightleftharpoons 2I_2$, is shifted to the right by the action of the solvent, which establishes a new equilibrium, $I_2 + S \rightleftharpoons SI_2$. Two main factors appear to determine the relative rates of iodine addition in the brown solutions, compared with the reactions in a solvent such as carbon tetrachloride : (*a*) the polarity of the solvent which tends to increase the rate, and (*b*) compound formation (S→I⁻I) which would be expected to decrease the rate. In a solvent such as *iso*butyl ether the second effect appears to be dominant, and rates are considerably less than in carbon tetrachloride, but in the more strongly polar nitrobenzene iodine addition is more rapid than in carbon tetrachloride.

The compounds on which the above conclusions are based included hex-1-ene, pent-2-ene, *cyclo*pentene, dec-1-ene, undecenoic acid, and oleic acid. With the concentrations examined, the iodine absorption at equilibrium was in the region of 90%, so that the influence of the back reaction is inconsiderable at the initial stages of the forward reaction. Other compounds, *e.g.*, *tert.*-butylethylene, 2-methylbut-1-ene, trimethylethylene, tetramethylethylene, gave on the attainment of equilibrium at similar concentrations a lower iodine absorption, so that such measurements could not conveniently be used for fixing the reaction order, or for investigating the influence of constitution on the rate of iodine addition.

The reactions of the above-mentioned compounds appeared to give equilibria which changed in accordance with the law of mass action, and varied in a regular way with the temperature. It was concluded, therefore, that the iodine addition, the kinetics of which were being investigated, was free from any accompanying polymerisation. But such disturbing effect in certain instances was found to be very considerable; reactions were observed to proceed with a rapid initial absorption, to show a temperature coefficient less than unity, and to give equilibria which varied in an irregular manner both with concentration and temperature. The substances that show such abnormalities are chiefly aromatic compounds, with a phenyl or substituted-phenyl group attached to the ethylene system, styrene, α-methylstyrene, αβ-dimethylstyrene, indene, 1 : 2-dihydronaphthalene, and anethole.

Reference is now made to the catalysis of iodine addition. Nozaki and Ogg (*J. Amer. Chem. Soc.*, 1942, **64**, 713) claim that hydrogen iodide is a powerful catalyst in acetic acid solution, although this is not evident from their quoted results. On taking precautions to remove traces of oxides from the unsaturated compounds, and making measurements in nitrogen atmosphere to prevent oxidation of the hydrogen iodide, we have found that hydrogen iodide reduces the rate of iodine addition to oleic acid and styrene and, if in sufficient concentration, completely inhibits the reaction. This corresponds with the effect of hydrogen bromide, which reduces the

rate of bromine addition to compounds containing electron-contributing groups, although it has the reverse effect if electron-attracting groups are present (*J.*, 1947, 630). Such a compound is propylpropiolic acid, and here there was found catalysis by hydrogen iodide, as hydrogen tri-iodide has become the nucleophilic reagent.

Nozaki and Ogg (*loc. cit.*) found that lithium chloride causes marked catalysis of iodine addition in acetic acid solution. We have confirmed this, and examined several other catalysts that are electrolytes in acetic acid (cf. table, *J.*, 1949, 295). It was indicated that the special reactivity of lithium chloride, which was much greater for iodine than for bromine under similar conditions, might be due to the formation of iodine chloride.

A preliminary examination has been made of the significance of the equilibria in reversible iodine addition. For the actual determination of the equilibrium constant of the reaction, the concentrations of the reactants were chosen to give approximately 50% iodine absorption, under which condition the experimental error is at a minimum. For the purpose of considering the relationship between such equilibria and the nature of different ethylene compounds, it is more realistic to present the results as relative iodine absorption for the same initial concentrations of reactants :

Percentage iodine absorption for M/4-A + M/50-I_2, *in acetic acid at* 25°.

$Me\cdot[CH_2]_2\cdot CH{:}CH_2$	$CH_2{:}CH\cdot[CH_2]_2\cdot CO_2H$	$CMe_2{:}CHMe$	$CMeEt{:}CH_2$	$CMe_2\cdot CH{:}CH_2$
98	96	64	39	14

*cyclo*Hexene	*cyclo*Pentene
85	51

The difference between trimethylethylene and 2-methylbut-1-ene and compounds of the type $CHR{:}CH_2$, and also the difference between the two cyclic compounds, suggest that a steric factor may operate to hinder the forward and favour the back reaction. With *tert.*-butylethylene there is the possibility of rearrangement of the positive carbon ion formed in the first phase of the addition :

$$Me_2C{-}\overset{+}{C}H{-}CH_2{-}\overline{I}{-}I \longrightarrow Me_2CH{-}CMeI{-}CH_2I$$

so that the significance of the equilibrium becomes ambiguous. Likewise bicyclic terpenes, such as norbornylene and camphene, in which the hindrance to *trans*-addition with inversion would be virtually complete, cannot be used as a diagnostic to test steric effects. With these two compounds the reactions proceed with complete absorption of iodine. This is consistent with the fact that such compounds undergo rearrangement on halogen addition with the production of 1 : 3-di-iodohydrocarbons, which do not dissociate, like the 1 : 2-derivatives, and iodine addition to norbornylene takes place at about the same rate as to *cyclo*pentene and *cyclo*hexene. As camphene adds iodine in chlorobenzene solution at a slower rate than *cyclo*hexene by a factor of about 25, and on the other hand adds bromine more rapidly by a factor of about 2 (unpublished work), for this compound there is a possibility of steric hindrance in the iodine reaction. α-Pinene, on the other hand, shows irregular kinetics and incomplete iodine absorption, corresponding with the fact that the reaction is more complex, cymene being known to be one of the products.

Experimental.

In the rate and equilibrium measurements sometimes the method of stopping the reaction with sodium thiosulphate and back-titrating with iodine was used, at other times it was found that the direct method of adding the reaction mixture to potassium iodide solution and titrating with sodium thiosulphate gave more consistent results. Herewith a typical measurement :

10 ml. of 1·08M-oleic acid + 0·208M-I_2 in CCl_4; 24°; 1 ml. added to 5 ml. of 0·01M-$Na_2S_2O_3$ and titrated with 0·103N-I_2.

Time (mins.)	0	1·7	3·2	5·2	6·6	8·6
Titre (ml. of I_2)	0·83	1·20	1·47	1·71	1·88	2·11

From the curve, $x = 20$, $t = 4{\cdot}5$; 2nd expt., $x = 20$, $t = 4{\cdot}6$.

Reactions in Acetic Acid Solution.—Undecenoic acid, previously examined at one concentration only, constant pseudo-bimolecular coefficients being obtained to $x = 50\%$ absorption, is now measured at the following concentrations :

% Reaction, x	10	20	30	40	50
Time (mins.) : 0·47M-A + 0·02M-I_2	2·2	5·0	7·5	12·5	18
,, 0·25M-A + 0·01M-I_2	9·5	22	34	49	72
Overall reaction order, n	3·1	3·1	3·1	3·0	3·0

Hydrogen iodide catalysis was examined with freshly distilled compounds, and in an inert atmosphere. A negative effect was obtained for compounds reacting by the electrophilic mechanism, and positive catalysis for propylpropiolic acid, which can react by a nucleophilic mechanism, as shown by the following reactions in acetic acid at 24° :

0·33M-Styrene + 0·0133M-I_2 + catalyst	None	0·0033M-HI	0·033M-HI
I_2 absorption (%, 50 mins.).....	17	7	0
0·33M-Oleic acid + 0·0133M-I_2 + catalyst	None	0·005M-HI	0·05M-HI
I_2 absorption (%, 10 mins.).....	59	32	0
0·33M-Propylpropiolic acid + 0·0133M-I_2 + catalyst ...	None	0·05M-HI	
I_2 absorption (%, 1400 mins.).....	6·6	31	

Reactions in Carbon Tetrachloride Solution.—Iodine addition in this solvent was found to be less sensitive to catalysis than bromine addition, and a change from air conditions to a sulphuric acid-dry nitrogen atmosphere did not appreciably alter the rates for pent-2-ene and oleic acid. On packing the vessel with glass-beads a slight acceleration was observed when the iodine concentration was small, but this effect disappeared at higher concentrations. It is concluded, therefore, that the high reaction orders to be recorded are for homogeneous iodine addition. The following results were obtained for oleic acid in carbon tetrachloride at 24° :

% Reaction, x	10	20	30	40
Time : 1·08M-A + 0·208M-I_2	1·8	4·5 •	8·0	13·2
,, 0·54M-A + 0·104M-I_2	10·3	30	54	85
Overall reaction order, n	3·5	3·6	3·6	3·7

• 14·5°, t = 5·4; 40°, t = 3·1; 25°, + $BaSO_4$, t = 0·9.

Experiments with 1·00M-oleic acid + 0·04M-I_2 and half these concentrations gave $n(x = 20) = 3·7$. The relative contributions of the reactants to the total order, calculated from the four runs are A, $n = 1·3$; I_2, $n = 2·4$. Pent-2-ene shows similar kinetics, giving at 16° reaction orders : A, $n = 1·3$; I_2, $n = 2·5$. For these two reactions in carbon tetrachloride the pseudo-bimolecular coefficients fall as the reaction proceeds, in accordance with the finding that the reaction order for iodine is greater than 2. The previously found constant pseudo-unimolecular values for allyl alcohol in this solvent are abnormal and possibly related to its association.

Reactions in Chlorobenzene.—Herewith are the results for *cyclo*pentene at 25°, as times for x = 20% iodine absorption : 0·25M-A + 0·02M-I_2, t = 3·5; 0·0125M-A + 0·01M-I_2, t = 29; 0·0125M-A + 0·02M-I_2, t = 7·8; hence A, $n = 1·1$; and I_2, $n = 2·9$. 0·25M-Camphene + 0·02M-I_2; 25°, x = 20, t = 246; norbornylene, same concns., 25°, x = 20, t = 4·2. The pseudo-bimolecular coefficients for this reaction, at $x = 10$, $k_2 = 3·7$, at $x = 60$, $k_2 = 2·2$, as there is no back reaction, indicate a reaction order, for A + I_2, >3.

The materials used were in part as described in earlier communications, and included also : pent-2-ene, b. p. 36—37°/760 mm.; trimethylethylene, b. p. 37—38°/741 mm.; tetramethylethylene, b. p. 72—73°/756 mm.; *cyclo*pentene, b. p. 44°/755 mm.; *cyclo*hexene, b. p. 82°/750 mm.; norbornylene, subliming at 52°; camphene, m. p. 43—44°.

We are indebted to the Ohio State University Research foundation for a valuable gift of 2-methylbut-1-ene, 3 : 3-dimethylbut-1-ene, and hex-1-ene, which were used in part for this investigation, and also to Dr. F. B. Shorland, Fats Research Department, Wellington, New Zealand, for pure specimens of oleic acid and methyl oleate.

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452. *Steroids and Related Compounds. Part IX. Further Experiments on the Bromination of Oxidation Products of Cholestane-3β : 5α : 6β-triol.*

By B. ELLIS and V. PETROW.

The processes of dehydrobromination and dehydration have been applied to 2-bromo-6-acetoxycholestan-5α-ol-3-one (III; R = Ac) and 2 : 2-dibromo-6-acetoxycholestan-5α-ol-3-one (V), but intermediates suitable for effecting the aromatisation of ring A have not been obtained.

WITH the object of effecting aromatisation of ring A of cholesterol, work was commenced in 1937 on the preparation of a 6-oxygenated cholesta-1 : 4-dien-3-one (I) from 6β-acetoxycholestan-5α-ol-3-one by the processes of bromination, dehydration, and dehydrobromination. The research had to be abandoned in 1938, the results obtained being reported in Part IV of this series (Ellis and Petrow, *J.*, 1939, 1078). The investigation has now been resumed, and we report some additional experiments.

Attempts to prepare (I) from (III; R = Ac) (Ellis and Petrow, *loc. cit.*) by removal of the elements of water and hydrogen bromide proved uniformly unsuccessful; *e.g.*, the compound was recovered unchanged after prolonged heating with acetic anhydride, after heating under reflux with 1·1 mols. of thionyl chloride in pyridine, and after treatment with dry hydrogen chloride in chloroform solution. Hot anhydrous formic acid led only to resinification. Dehydrobromination was next examined but, although reagents such as boiling collidine gave bromine-free products, these could not be induced to crystallise.

Experiments were therefore initiated on the preparation of (XVI) which possesses the structural features of cholestan-5α-ol-3 : 6-dione, a diketo-alcohol which is known to undergo ready dehydration (Pickard and Yates, *J.*, 1908, **93**, 1681). Oxidation of (III; R = H) offered the best potential route to this compound, but hydrolysis of (III; R = Ac) to the required alcohol proved unsuccessful. Reaction with alkali has already been shown to give the 2 : 5-oxide (Part IV, *loc. cit.*). Reaction with alcoholic hydrochloric acid has now been found to give cholest-4-en-3 : 6-dione (IV), formed, no doubt, through the intermediate formation of 2-bromocholestane-3 : 6-dione ⟶ 4-bromocholestane-3 : 6-dione ⟶ (IV) [cf. 6β-acetoxycholestan-5α-ol-3-one ⟶ cholestane-3 : 6-dione, Ellis and Petrow (*loc. cit.*); also (X) ⟶ (IV) (Experimental section)]. Attempts to prepare the required compound (XVI) by direct bromination of cholestan-5α-ol-3 : 6-dione (XIV) proved more encouraging. Treating (XIV) in chloroform–acetic acid solution with one molar equivalent of bromine gave a mixture of products from which unchanged (XIV), 4 : 7 : 7-tribromocholest-4-en-3 : 6-dione (XV) (Butenandt *et al.*, *Annalen*, 1937, **531**, 176), and a new monobromide, $C_{27}H_{44}O_2Br$, were isolated. The last compound differed from the 7-bromocholestan-5α-ol-3 : 6-dione of Sarett, Chakravorty, and Wallis (*J. Org. Chem.*, 1943, **8**, 405) and is regarded as 2-bromocholestan-5α-ol-3 : 6-dione (XVI). Its preparation gave erratic results and was only occasionally successful. This fact, coupled with the unsatisfactory yields obtained, precluded its further examination.

Accordingly, we turned our attention to the reactions of 2 : 2-dibromo-6β-acetoxycholestan-5α-ol-3-one, hoping thereby to obtain an intermediate suitable for conversion into (I).

Dibromination of (II) or monobromination of (III; R = Ac) is known to yield a dibromo-compound regarded as 2 : 2-dibromo-6β-acetoxycholestan-5α-ol-3-one (V) (Ellis and Petrow, *loc. cit.*). In striking contrast to its monobromo-analogue (III; R = Ac) (see above), (V) has now been found to undergo ready dehydration on simply heating it with acetic anhydride or acetic acid, to give an unsaturated compound formulated as 2 : 2-dibromo-6β-acetoxycholest-4-en-3-one (VI) on the basis of (*a*) its ultra-violet absorption spectrum, which shows a band at 250 mμ. compatible with its formulation as a dibromo-3-ketocholest-4-ene derivative, and (*b*) its conversion into a quinoxaline derivative.

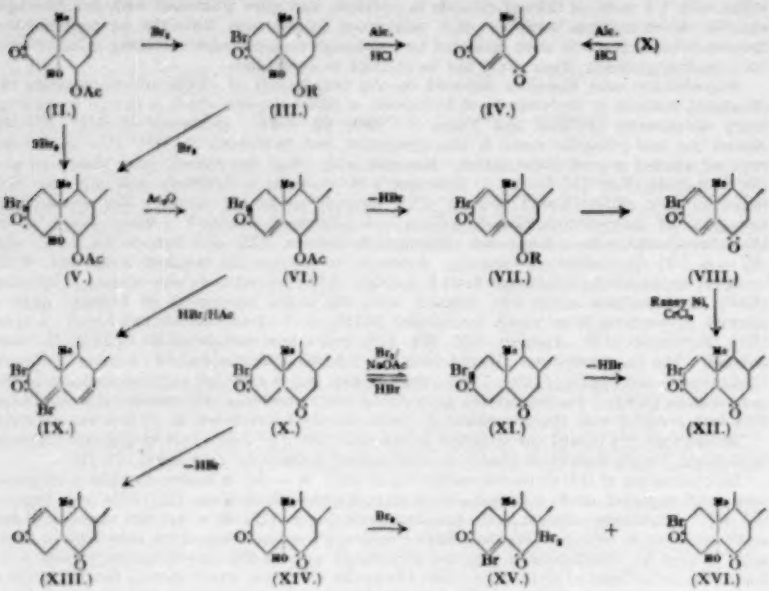
Although the dibromide (V) was sparingly soluble in acetic acid and separated from solution during preparation, it slowly redissolved when the reaction mixture was kept at room temperature for several hours. The solution now contained a new dibromo-ketone, $C_{27}H_{44}OBr_2$, also obtained by treating 2 : 2-dibromo-6β-acetoxycholest-4-en-3-one (VI) with hydrobromic acid–acetic acid and evidently formed from it by loss of the elements of acetic acid.

The new dibromo-ketone failed to liberate iodine from sodium iodide in benzene–alcoholic solution on warming, or to form a quinoxaline derivative with *o*-phenylenediamine. These observations exclude a 2 : 2-dibromo-formulation. Its ultra-violet absorption spectrum revealed a maximum at 292·5 mμ. and a minimum at 235·0 mμ., and this indicated a cholesta-4 : 6-dien-3-one containing substituent bromine atoms (see Jackson and Jones, *J.*, 1940, 569). The constitution of a 2 : 4-dibromocholesta-4 : 6-dien-3-one (IX) has therfore been assigned to this compound. Similar transformations of 2 : 2-dibromo-3-keto-steroids of the 5-*allo*-series into the corresponding 2 : 4-dibromoketones under the influence of hydrobromic acid–acetic acid have previously been reported (see Djerassi and Scholz, *J. Amer. Chem. Soc.*, 1947, **69**, 2404), and the elimination of the acetoxy-grouping from (VI) is paralleled by the conversion of 3β-acetoxycholest-5-en-7-one into cholesta-3 : 5-dien-7-one (Jackson and Jones, *loc. cit.*). 6β-Acetoxycholest-4-en-3-one (Part IV, *loc. cit.*), in contrast, gives only the saturated cholestane-3 : 6-dione on treatment with hydrobromic acid.

Monodehydrobromination of (VI) was readily accomplished with boiling collidine, a 2-bromo-6β-acetoxycholesta-1 : 4-dien-3-one (VII; R = Ac) being obtained in excellent yield. Attempts to convert this compound into (I), however, proved unsuccessful. Thus it was unaffected by chromous chloride in acetone (see Julian *et al.*, *J. Amer. Chem. Soc.*, 1945, **67**, 1728) or by zinc (Inhoffen and Zuchlsdorf, *Ber.*, 1943, **76**, 233) or Raney nickel in boiling alcohol.

Hydrolysis of (VII; R = Ac) with methanolic potash, followed by oxidation, gave 2-bromocholesta-1 : 4-dien-3 : 6-dione (VIII), but this dione, too, was recovered unchanged after

prolonged treatment with zinc dust in alcohol. Raney nickel or chromous chloride, however, led to partial reduction with formation of a bromocholesten-3 : 6-dione, m. p. 221°, identical



with a compound (m. p. 204—207°) obtained by Sarett and co-workers (*loc. cit.*) by the action of boiling pyridine on 2 : 2-dibromocholestan-3 : 6-dione (XI) and assigned by them the constitution of a 2-bromocholest-4-en-3 : 6-dione. We are unable to accept this formulation on the following evidence : (i) the ultra-violet absorption spectrum reveals a maximum at 257 mμ. characteristic of 2-bromocholest-1-en-3-ones which are now known to form an exception to Woodward's rule (*J. Amer. Chem. Soc.*, 1941, **63**, 1123; 1942, **64**, 76) (see Djerassi and Scholz, *loc. cit.*); (ii) the compound is recovered unchanged after prolonged heating with collidine, a behaviour hardly consistent with a 2-bromo-Δ^4-structure. Accordingly, we assign the constitution of a 2-bromocholest-1-ene-3 : 6-dione (XII) to this product. Cholest-4-ene-3 : 6-dione (IV), it may be added, likewise readily undergoes reduction to cholestane-3 : 6-dione on treatment with the chromous chloride reagent, a reaction which furnishes a convenient route to this saturated diketone.

Attempts to reduce (XII) with zinc in alcohol proved unsuccessful, a somewhat surprising result, since Djerassi and Scholz (*loc. cit.*) have achieved smooth conversion of the analogous 2-bromo-3-ketoandrost-1-en-17α-yl 17-hexahydrobenzoate into the corresponding androst-1-en-3-one derivative under similar experimental conditions. These authors describe the conversion of the same hexahydrobenzoate into the 4-bromo-Δ^1-ketone by treatment with hydrobromic acid–acetic acid. Similar isomerisation of (XII) would clearly furnish a key intermediate for the preparation of (I), but the compound failed to react in the required way and was recovered unchanged.

Lastly, the action of hydrobromic acid–acetic acid on (XI) was examined when it was hoped to effect conversion into the corresponding 2 : 4-dibromo-derivative. Unfortunately, only reduction occurred to give a 2-bromocholestane-3 : 6-dione (X). The position of the bromine atom in this compound followed from the observation that dehydrobromination gave a new αβ-unsaturated ketone, $\lambda_{max.} = 228$ mμ., not identical with (IV), which we believe to be cholest-1-ene-3 : 6-dione (XIII).

Experimental.

(M. p.s are uncorrected. Microanalyses are by Drs. Weiler and Strauss, Oxford. Rotations were measured in chloroform solution in a 2-dm. tube unless otherwise stated. Absorption spectra, measured in *iso*propyl-alcoholic solution, were kindly determined by Dr. R. E. Stuckey and Mr. P. Stross, B.Sc., Analytical Department, The British Drug Houses Ltd.)

Acid Hydrolysis of 2-*Bromo*-6β-*acetoxycholestan*-5α-*ol*-3-*one*.—Finely powdered (III; R = Ac) (2 g.) in boiling ethanol was treated with concentrated hydrochloric acid (2·0 ml.), added under reflux. After 5 hours the product, cholest-4-ene-3 : 6-dione (IV), was precipitated with water; it formed faintly yellow plates (from aqueous ethanol), m. p. 122—123° (Found : C, 81·2; H, 10·3. Calc. for $C_{27}H_{42}O_2$: C, 81·3; H, 10·6%), not depressed in admixture with an authentic specimen.

Bromination of Cholestan-5α-*ol*-3 : 6-*dione* (XIV).—(XIV) (2·08 g.) in chloroform (100 ml.) and acetic acid (10 ml.) at 28° was treated with bromine (880 mg., 1·1 mols.) in acetic acid (10 ml.), absorption being complete within 1 minute. After immediate addition of excess of sodium acetate solution, the non-aqueous layer was removed, washed, and dried, and the solvent distilled off. The residue, in acetone (30 ml.), was cooled strongly and fraction A, m. p. 180° (decomp.) (400 mg.), separated and was removed. Cautious dilution of the filtrate gave fraction B, m. p. 209° (decomp.) (400 mg.), followed by fraction C (600 mg.) (a gum which slowly crystallised). Purification of fraction A from acetic acid gave unchanged starting material. Crystallisation of fraction B from aqueous acetone and alcohol gave 2-*bromocholestan*-5α-*ol*-3 : 6-*dione* in leafy plates, m. p. 238° (decomp.), $[\alpha]_D^{18}$ −22·6° (*c*, 1·89; *l*, 1) (Found : C, 65·4; H, 8·6; Br, 15·5. $C_{27}H_{43}O_3Br$ requires C, 65·5; H, 8·7; Br, 16·1%). Fraction C, after purification from aqueous acetone, gave thin needles of 4 : 7 : 7-tribromocholest-4-ene-3 : 6-dione, m. p. 195° (decomp.), $[\alpha]_D^{18}$ +15·2° (*c*, 1·41) (Found : C, 51·1; H, 6·4. Calc. for $C_{27}H_{39}O_2Br_3$: C, 51·0; H, 6·2%), not depressed in admixture with an authentic specimen (Butenandt *et al.*, *Annalen*, 1937, **531**, 176).

Bromination in the presence of excess of sodium acetate gave a complex mixture of products from which only unchanged material could be isolated.

2 : 3-*Dibromo*-6β-*acetoxycholest*-4-*en*-3-*one* (VI).—When 2 : 2-dibromo-6-acetoxycholestan-5α-ol-3-one (V) was heated under reflux with acetic anhydride (8·5 vols.) for 2½ hours, or acetic acid for 1 hour, 2 : 2-*dibromo*-6β-*acetoxycholest*-4-*en*-3-*one* was obtained, hard needles (from aqueous acetone), m. p. 154—155°, $[\alpha]_D^{18}$ −10·8° (*c*, 1·8) (Found : C, 58·5; H, 7·1. $C_{29}H_{44}O_4Br_2$ requires C, 58·0; H, 7·3%); yield 50%. Light absorption : $E^{1\%}_{1cm}$ (250 mμ.) = 157. The *quinoxaline* derivative, prepared by heating the dibromo-ketone (1·0 g.) and *o*-phenylenediamine (1 g.) in absolute ethanol (25 ml.) under reflux for 6 hours, formed thin plates (from aqueous acetone), m. p. 204° (Found : N, 5·6. $C_{33}H_{44}O_3N_2$ requires N, 5·3%).

2 : 4-*Dibromocholesta*-4 : 6-*dien*-3-*one* (IX).—(*a*) 6-Acetoxycholestan-5α-ol-3-one (2·3 g.) in acetic acid (50 ml.) was treated with bromine (1·6 g.) in acetic acid (9 ml.). Rapid decolorisation occurred, followed by separation of (V), which slowly dissolved, dissolution being complete in 18 hours. Precipitation with water and extraction with ether gave 2 : 4-*dibromocholesta*-4 : 6-*dien*-3-*one*, flat needles (from methanol–acetone), m. p. 178° (decomp.), $[\alpha]_D^{18}$ +37·8° (*c*, 2·38; *l*, 1) (Found : C, 60·2, 59·9; H, 7·0, 7·3. $C_{27}H_{40}OBr_2$ requires C, 60·0; H, 7·5%). The absorption spectrum showed a maximum at 292·5 mμ. ($E^{1\%}_{1cm}$ = 270) and a minimum at 235 mμ. ($E^{1\%}_{1cm}$ = 134). (*b*) 2 : 2-Dibromo-6-acetoxycholestan-5α-ol-3-one (1·0 g.) in glacial acetic acid (30 ml.) containing hydrobromic acid (1 ml. of 48%) was heated under reflux for 3 minutes. Precipitation with water gave (IX), identified by m. p. and mixed m. p. (*c*) Treatment of 2 : 2-dibromo-6-acetoxycholest-4-en-3-one (VI) with hydrobromic acid–acetic acid as in (*b*) likewise gave (IX). The compound occasionally separated from aqueous acetone in a polymorphic form, m. p. 154° (decomp.). A mixture of the two forms softened at 154° and melted with decomposition at 178°.

Action of Hydrobromic Acid–Acetic Acid on 6β-*Acetoxycholest*-4-*en*-3-*one*.—When the ketone (500 mg.) in acetic acid (15 ml.)–hydrobromic acid (0·7 ml. of 48%) was left at 37° for 18 hours and the carmine-coloured solution was diluted with water, cholestane-3 : 6-dione (200 mg.) was obtained, identified after crystallisation from aqueous acetone by m. p. and mixed m. p. with an authentic specimen.

2-*Bromo*-6-*acetoxycholesta*-1 : 4-*dien*-3-*one* (VII; R = Ac).—When 2 : 2-dibromo-6-acetoxycholest-4-en-3-one (19·7 g.) was heated under reflux with collidine (100 ml.) for 7 minutes, 2-*bromo*-6-*acetoxycholesta*-1 : 4-*dien*-3-*one* was obtained, hard prismatic needles from aqueous acetone, m. p. 123—124°, $[\alpha]_D^{18}$ −32·3° (*c*, 1·15) (Found : C, 66·9; H, 8·3. $C_{29}H_{41}O_3Br$ requires C, 67·1; H, 8·3%); yield 82%. Light absorption : $E^{1\%}_{1cm}$ (253 mμ.) = 248.

2-*Bromocholesta*-1 : 4-*dien*-6β-*ol*-3-*one* (VII; R = H).—A solution of potassium hydroxide (1·4 g.) in 95% methanol (25 ml.) was added rapidly to a boiling solution of the foregoing compound (11·7 g.) in methanol (200 ml.). Separation of crystalline material began almost immediately and this was collected when the mixture was cold, giving 2-*bromocholesta*-1 : 4-*dien*-6β-*ol*-3-*one*, large shining plates (from aqueous acetone), m. p. 240°, $[\alpha]_D^{18}$ −37·8° (*c*, 1·06) (Found : C, 68·1; H, 8·7. $C_{27}H_{41}O_2Br$ requires C, 67·9; H, 8·6%); yield 90%. Light absorption : $E^{1\%}_{1cm}$ (255 mμ.) = 305. Acetylation gave (VII; R = Ac), m. p. 123—124°.

2-*Bromocholesta*-1 : 4-*diene*-3 : 6-*dione* (VIII).—Chromic acid (600 mg.) in acetic acid (10 ml. of 90%) was added to a stirred suspension of the finely powdered foregoing compound (2·0 g.) in acetic acid (60 ml.) at 75°. After 7 minutes, excess of brine was added, and the precipitated solids were collected and crystallised from aqueous acetone, giving 2-*bromocholesta*-1 : 4-*diene*-3 : 6-*dione* in leafy plates, m. p. 182°, $[\alpha]_D^{18}$ −139° (*c*, 1·74) (Found : C, 68·1; H, 8·1. $C_{27}H_{39}O_2Br$ requires C, 68·2; H, 8·2%); yield 60%. The absorption spectrum showed a maximum at 255 mμ. ($E^{1\%}_{1cm}$ = 234) and a minimum at

232 mμ. ($E^{1\%}_{1cm.}$ = 139). The dione was recovered unchanged after being refluxed with zinc dust in alcohol for 10 hours.

2-Bromocholest-1-ene-3 : 6-dione (XII).—(*a*) Alcoholic chromous chloride solution (10 ml.) (Conant and Cutler, *J. Amer. Chem. Soc.*, 1926, **48**, 1023) was added, under carbon dioxide, to 2-bromocholesta-1 : 4-diene-3 : 6-dione (500 mg.) in acetone (30 ml.), and the mixture kept for 45 minutes at room temperature. The product, isolated with ether, was fractionated from aqueous acetone, giving *form A* of 2-bromocholest-1-ene-3 : 6-dione in silvery platelets, m. p. 221°, $[\alpha]_D^{20}$ −61° (*c*, 1·64; *l*, 0·5) (Found: C, 67·6; H, 8·5. $C_{27}H_{41}O_2Br$ requires C, 67·9; H, 8·7%); yield 30%. Careful dilution of the mother-liquors gave *form B*, fine needles, m. p. 160—162°, $[\alpha]_D^{20}$ −63° (*c*, 1·1; *l*, 1) (Found: C, 68·1; H, 8·5%); yield 50%. Forms A and B gave identical absorption spectra: $E^{1\%}_{1cm.}$ (257 mμ.) = 156.

(*b*) Form A, m. p. 221°, was obtained when (VIII) (500 mg.) was heated under reflux for 18 hours with Raney nickel (*ca.* 500 mg.) in ethanol (7 ml.).

(*c*) 2 : 2-Dibromocholestane-3 : 6-dione (1·1 g.) was heated under reflux with collidine (5 ml.) for 1·5 minutes, and collidine hydrobromide (403 mg. = 1·0 atom bromine) removed after addition of ether. The ethereal solution was washed with dilute hydrochloric acid, etc., and the dark product chromatographically purified on alumina (B.D.H. for chromatographic analysis). The column (12 × 1·4 cm.) was prepared in light petroleum (b. p. 40—60°). A crystalline fraction (200 mg.) was obtained by elution with benzene–light petroleum (4 : 1). Its purification gave form A, m. p. 220—221°, alone or in admixture with an authentic specimen. The same product was obtained when pyridine was employed in place of collidine as described by Sarett *et al.* (*loc. cit.*).

The compound (XII) was recovered unchanged after (*a*) 18 hours' heating under reflux with zinc dust in ethanol, and (*b*) treatment with hydrobromic acid–acetic acid for 24 hours at room temperature.

Reduction of Cholest-4-ene-3 : 6-dione.—The compound (400 mg.) in acetone (10 ml.) was treated with chromous chloride (10 ml.) under carbon dioxide. After 10 minutes the crystalline solids (250 mg.) were collected and purified from aqueous ethanol, giving cholestane-3 : 6-dione, m. p. 169—170°, alone or in admixture with an authentic specimen.

2-Bromocholestane-3 : 6-dione (X).—A suspension of 2 : 2-dibromocholestane-3 : 6-dione (5·25 g.) in chloroform (40 ml.) and acetic acid (75 ml.) containing hydrobromic acid (2 ml. of 48%) was shaken for 4 hours. The product, isolated with ether, was crystallised from aqueous acetone, giving *2-bromocholestane-3 : 6-dione* in needles, $[\alpha]_D^{20}$ −10·4° (*c*, 1·5) (Found: C, 67·5; H, 8·8. $C_{27}H_{43}O_2Br$ requires C, 67·6; H, 9·0%); yield 20%. The m. p. (decomp.) varied from sample to sample and with the rate of heating, decomposition usually occurring at 140—180°. The absorption spectra of different preparations revealed the presence of variable small amounts of an impurity absorbing at 252 mμ. Reduction of (X) with chromous chloride furnished cholestane-3 : 6-dione in good yield, and refluxing it with alcoholic hydrochloric acid gave cholest-4-en-3 : 6-dione.

2 : 2-*Dibromocholestane-3 : 6-dione* (XI).—The foregoing compound (1·1 g.) in acetic acid (20 ml.) and chloroform (5 ml.) was treated with bromine (400 mg., 1·1 mols.) in acetic acid (5 ml.) containing sodium acetate (300 mg.). After 6 hours at room temperature the product (350 mg.) was collected and crystallised from chloroform–ethyl acetate, giving 2 : 2-dibromocholestane-3 : 6-dione in micro-needles which decomposed between 175° and 195°; $[\alpha]_D^{20}$ +68·3° (*c*, 1·31) (Found: C, 57·9; H, 8·1. Calc. for $C_{27}H_{42}O_2Br$: C, 58·1; H, 7·6%). Sarett *et al.* (*loc. cit.*) give a decomposition temperature of 175—195° and $[\alpha]_D^{20}$ +65°.

Cholest-1-ene-3 : 6-dione (XIII).—2-Bromocholestane-3 : 6-dione (1·1 g.) was heated under reflux with collidine (8 ml.) for 15 minutes. After addition of ether, collidine hydrobromide and a *compound*, small plates (from acetic acid), m. p. >300° (Found: N, 2·0. $C_{11}H_{15}O_2NBr$ requires N, 2·3%), were removed, leaving *cholest-1-ene-3 : 6-dione*, plates (from aqueous ethanol), m. p. 161° (Found: C, 79·7; H, 10·1. $C_{27}H_{44}O_2,\frac{1}{2}H_2O$ requires C, 79·6; H, 10·6%). Light absorption: $E^{1\%}_{1cm.}$ (228 mμ.) = 200.

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453. *Constituents of the Seeds of* Corchorus olitorius, *L. Part I. Corchorin and its Identity with Strophanthidin.*

By Gabra Soliman and (in part) Wahba Saleh.

Corchorin, the crystalline bitter principle of jute seeds, is isolated from the seeds of *Corchorus olitorius*, L., and is shown to have the formula $C_{23}H_{32}O_6$ and to be identical with strophanthidin.

The occurrence of a bitter principle, corchorin, in the seeds of *Corchorus capsularis*, L. (Tiliaceæ), commonly known as jute, was first reported by Tsuno (*Monatsh. Tierheilk.*, 1896, **6**, 455), and later corchorin was described by Friebos (Dissert., Rostock; *Jahr. Pharm.*, 1907, 102) as a whitish, crystalline bitter substance. Furthermore, Kobert ("Lehrbuch der Intoxikationen," 1906, p. 1222; *Chem. Zentr.*, 1907, **1**, 1273), who was provided with an

impure specimen of corchorin by Merck, recorded its pharmacological action and described its chemical and physical properties without mentioning its melting point or percentage composition.

The isolation of an isomeric, if not identical, bitter compound, capsularin, $C_{32}H_{44}O_9$, m. p. 175—176°, from jute leaves was achieved by Saha and Choudhury (*J.*, 1922, 1044), but present knowledge regarding the isolation and analysis of corchorin of jute seeds is largely due to Sen (*J. Indian Chem. Soc.*, 1930, **7**, 83). Corchorin is described by this author as whitish rhombic prisms, m. p. 174—175°, having an intense bitter taste. It develops, with concentrated sulphuric acid, a red colour with green fluorescence, and yields glucose and corchogenin, m. p. 112—114°, on hydrolysis. Sen (*ibid.*, p. 905) assigned to corchorin and corchogenin the formulæ, $C_{32}H_{54}O_9$ and $C_{14}H_{24}O_3$, respectively.

As corchorin is recorded in the literature as a cardiac glycoside (Rijn and Dieterle, " Die Glycoside," 1931, p. 317, Verlag Borntraeger, Berlin), and as the seeds of *Corchorus olitorius*, L. (Tiliaceæ), are recognised among Egyptian peasants as poisonous to cattle, whereas the plant is widely cultivated in Egypt for use as a pot herb, under the name " Melukhiya," it seemed of interest to attempt the isolation of such a glycoside from this plant. We have isolated corchorin (the properties of which suggest a genin, not a glycoside) from the alcoholic extract of the defatted seeds of *Corchorus olitorius*. Previously, the plant and its seeds were studied microscopically and chemically by Amin, Fahmy, and Fahmy (*Report Pharm. Soc., Egypt*, 1934, **6**, 12), and the occurrence of a glycosidic principle in the alcoholic extract of the defatted seeds was indicated by chemical tests. Corchorin, obtained by the method described in the experimental, crystallised from dilute methanol in rhombic prisms, m. p. 175—177° (decomp.) not depressed with an authentic specimen prepared from jute seeds.

Contrary to Saha and Choudhury (*loc. cit.*) and Sen (*locc. cit.*) we were unable to hydrolyse corchorin with 2% sulphuric acid solution, or with varying concentrations of hydrogen chloride in dilute alcohol. In certain cases the starting material was recovered unchanged, otherwise it suffered resinification without the elimination of a sugar moiety. Additional disagreement lies in the fact that we have prepared from corchorin, from either of the two species of *Corchorus*, a crystalline acetate, m. p. 242—244° (decomp.), whereas capsularin acetate and corchorin acetate were assigned by Saha and Choudhury (*loc. cit.*) and Sen (*locc. cit.*) the melting points 190° and 158°, respectively, and the formula, $C_{32}H_{51}O_9Ac_3$.

The results of analysis of our dehydrated specimens of corchorin and its acetate indicate the formulæ, $C_{32}H_{52}O_8$ and $C_{32}H_{51}O_8Ac$, and the presence of an αβ-unsaturated lactone group was shown by titration with standard alkali, by the formation of a red colour in the Légal sodium nitroprusside test, and by reduction of Tollens's reagent (Jacobs and Hoffmann, *J. Biol. Chem.*, 1925, **67**, 333; Haynes, *Quart. Reviews*, 1948, **2**, 46). In addition to the lactone group and the hydroxyl group which can be acetylated, the presence of a carbonyl group in corchorin is shown by the formation of an oxime, $C_{32}H_{53}O_8N$, m. p. 265—270° (decomp.), and a phenylhydrazone, $C_{38}H_{56}O_7N_2$, m. p. 240—243°; the remaining two oxygen atoms appear to be present in tertiary hydroxyl groups. The formulæ, melting points, and properties of corchorin and its derivatives are in agreement with those of strophanthidin. Full identity of the two lactones was established by comparison with authentic specimens (cf. Jacobs *et al.*, *J. Biol. Chem.*, 1922, **54**, 253; 1924, **59**, 713; 1927, **74**, 805; Lamb and Smith, *J.*, 1936, 444; Steidt, Anderson, and Chen, *Proc. Soc. Expl. Biol. Med.*, 1943, **53**, 198; *J. Pharm. Expl. Ther.*, 1944, **82**, 98).

It would be of a biogenetic interest should the presence of a strophanthin glycoside be proved in the bitter mother-liquor from which corchorin has been isolated, or in the extracts of the immature seeds or other parts of the plant. At present, attempts are being made along these lines and towards the elucidation of the structure of another bitter compound, corchoritin, m. p. 218—220°, which was described by Sen (*J. Indian Chem. Soc.*, 1931, **8**, 651) as a hydroxylactone, $C_{12}H_{14}O_3$. Moreover, the alcoholic extract of the defatted seeds of *Corchorus olitorius* yielded a solid from which raffinose (cf. Sen, *locc. cit.*; Annett, *Biochem. J.*, 1917, **11**, 192) and a tasteless resin were separated. On successive crystallisations of the latter, a phenolic compound, m. p. 103—105°, was obtained, and the results of its investigation will be communicated later.

Experimental.

(M. p.s are not corrected; micro-analyses were by Drs. Weiler and Strauss, Oxford, and unless otherwise stated the analytical specimens were dried (and dehydrated) at 110° in a high vacuum over phosphoric oxide.)

Extraction.—The powdered seeds of *Corchorus olitorius* (obtained from the Minia district in Upper Egypt) were extracted three times with light petroleum (b. p. 60—80°). The combined extracts yielded

on evaporation a dark greenish oil (14—15%) which deposited a waxy solid when kept in the ice-chest. The defatted meal (5 kg.) was refluxed with alcohol for about 8 hours and the liquid filtered hot; this process was repeated twice and, after cooling, the yellow-brown deposit was separated from the combined filtrates. By successive concentration and cooling, more of the yellow-brown deposit (" A ") (300 g.) was collected. Finally, the extract was freed from most of its alcoholic content by distillation under reduced pressure on the water-bath, and a dark brown, bitter syrup (" B ") was left.

Isolation of Corchorin.—The syrup " B " (2 l.) was diluted with hot water (1·5 l.), clarified by filtration, and mixed with basic lead acetate (150 g.) in hot water (500 ml.), then the mixture was kept overnight at room temperature. After the mixture had been filtered excess of lead was removed from the filtrate by hydrogen sulphide, and the clear solution concentrated under reduced pressure on the water-bath to about 2 l. At this stage, corchorin began to separate as small crystals (12 g.), m. p. 162—165°, which lost most of their bitter taste on crystallisation (charcoal) from dilute methanol or ethanol. Pure corchorin is readily soluble in methanol, ethanol, or pyridine, is sparingly soluble in water, chloroform, or benzene, and crystallises from dilute methanol in whitish rhombic prisms, m. p. 175—177° (decomp.), solidifies and remelts at 235°, and does not depress the melting points of corchorin from jute seeds or strophanthidin [Found, in specimens dried over phosphoric oxide: C, 66·8, 66·8; H, 8·1, 8·2%; *M* (by titration), 410·5, 418·6. Calc. for $C_{29}H_{44}O_9,\frac{1}{2}H_2O$: C, 66·8; H, 8·1%; *M*, 413·3], $[\alpha]_D^{20}$ +40·6° (*c*, 7·350 in methanol) [Found in dehydrated specimens: C, 68·3, 68·3; H, 8·0, 7·9%; *M* (Rast), 396; *M* (by titration), 404·2, 408·1. Calc. for $C_{29}H_{44}O_9$: C, 68·3; H, 8·6%; *M*, 404·3], $[\alpha]_D^{20}$ +42·7° (*c*, 3·845 in methanol). It dissolves in concentrated sulphuric acid to a red solution with a green fluorescence, and its solution in alcohol or pyridine becomes red on the addition of sodium nitroprusside and sodium hydroxide solutions; it readily reduces Tollens's reagent. The acetate was prepared by heating corchorin (0·5 g.) in pyridine–acetic anhydride (10 ml.; 1 : 1) for two hours on the water-bath, the solution was concentrated by distillation under reduced pressure at a low temperature, and the residue was crystallised from dilute methanol, and recrystallised from benzene–methanol; it formed prisms, m. p. 242—244° (decomp.) (Found: C, 67·3, 67·4; H, 7·6, 7·7. Calc. for $C_{33}H_{48}O_{10}$: C, 67·2; H, 7·7%), $[\alpha]_D^{20}$ +39·30° (*c*, 3·051 in methanol). The oxime crystallised from alcohol in rhombic prisms, m. p. 265—270° (decomp.), identical with strophanthidin oxime (Found: C, 66·0, 65·7; H, 8·1, 8·0; N, 3·3, 3·4. Calc. for $C_{29}H_{45}O_9N$: C, 65·8; H, 7·9; N, 3·3%). The phenylhydrazone crystallised from ethyl acetate in colourless prisms, m. p. 240—243° (cf. Thoms and Unger, *Z. angew. Chem.*, 1924, **37**, 721) (Found: C, 70·1; H, 7·7; N, 5·6. Calc. for $C_{35}H_{48}O_9N_2$: C, 70·4; H, 7·8; N, 5·7%).

For comparison, corchorin was prepared by extraction of the seeds (2 kg.) of *Corchorus capsularis*; the product (0·2%) crystallised from dilute methanol in rhombic prisms, m. p. 175—177° (decomp.) (Found in specimens dried over phosphoric oxide: C, 66·8, 67·0; H, 8·1, 8·3%. Found in dehydrated specimens: C, 68·3, 68·2; H, 8·1, 8·2%), $[\alpha]_D^{20}$ +42·5° (*c*, 0·642 in methanol). It gave an acetate, m. p. 242—244° (decomp.) (Found: C, 67·2; H, 7·7%). Sen's results are C, 61·6; H, 8·5%; $[\alpha]_D$ +33·4° in ethanol for corchorin, and C, 60·4; H, 7·0% for its acetate.

When the solid deposit " A " was refluxed with ethyl acetate, the fluorescent solution deposited a yellowish-brown resinous product on cooling, and the insoluble gummy residue gave on crystallisation from 90% alcohol white rhombic crystals, m. p. 75°, identical with raffinose. After several crystallisations of the resinous product from ethyl acetate and then from benzene, a substance, m. p. 103—105°, was obtained and characterised by the formation of a green colour with ferric chloride and a colourless acetate, m. p. 74°.

The authors are indebted to Professor G. A. R. Kon, F.R.S., for a specimen of strophanthidin, and to the Egyptian Ministry of Agriculture for providing the seeds of *Corchorus capsularis*.

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454. *The Formation of Complex Fluorides. Part I. The Relation between the Conductivities of Boric, Arsenious, and Antimonic Fluorides and Complex Formation.*

By A. A. Woolf and N. N. Greenwood.

The formation of alkali complex fluorides by addition and neutralisation reactions in non-aqueous solutions is discussed in relation to the conductivity of the fluorides used as solvents. The specific conductivities of boron trifluoride, arsenic trifluoride, and antimony pentafluoride are $< 5 \times 10^{-10}$ (at −120°), $2{\cdot}4 \times 10^{-4}$ (at 25°), and $1{\cdot}2 \times 10^{-4}$ (at 25°) ohm^{-1} $cm.^{-1}$ respectively. The possible ionic nature of the double fluorides formed by Group-Vb and -VIIb fluorides, including the new compounds $AsF_3.SbF_5$ and $IF_5.SbF_5$, is mentioned, and the viscosities of arsenic trifluoride and antimony pentafluoride are reported.

Complex fluorides of the alkali and alkaline-earth metals can be prepared either by gas–solid reactions or by reactions in solution. The former, because of their high activation energies, are carried out at high temperatures and sometimes at high pressures and consequently are only applicable to the thermally stable complexes. The combination of sodium fluoride with boron

trifluoride, for example, although noticeable at room temperature, is quantitative at 400° (De Boer and van Liempt, *Rec. Trav. chim.*, 1927, **46**, 124). Similarly, potassium fluoride and uranium hexafluoride combine in equimolecular proportions at 200° under 70 atmospheres' pressure (Martin and Albers, *Naturwiss.*, 1940, **28**, 370). Direct fluorination is an alternative gas–solid reaction which has been used to produce a salt-like product (presumably $NaOsF_6$) from sodium fluoride and osmium (Ruff and Tschirch, *Ber.*, 1913, **46**, 929). Klemm and Huss (*Z. anorg. Chem.*, 1949, **258**, 221) have recently used similar reactions to prepare K_2CoF_4, K_2NiF_4, and K_2CuF_4 from mixtures of the corresponding chlorides.

Reactions in solution can occur at much lower temperatures since in these reactions less energy is required to disrupt the crystal lattice than is required in non-solvent reactions because of the partial compensation provided by the solvation energy. Anhydrous and aqueous hydrogen fluoride are the common solvents, and bromine trifluoride has recently been used to prepare a wide range of complex fluorides (Woolf and Emeléus, *J.*, 1950, 1050).

There appears to be a relation between complex formation in solution and the electrical conductivity of the anion component fluoride. The conductivities of the " covalent " fluorides so far examined fall into two groups. The fluorides of the first group have conductivities of at least 10^{-4}ohm^{-1} cm.$^{-1}$, and it is these fluorides which form complexes with the alkali fluorides in solution. Thus arsenic trifluoride, bromine trifluoride, iodine pentafluoride, and hydrogen fluoride, which with potassium fluoride form $KAsF_4$, $KBrF_4$, KIF_4, and KHF_2 respectively, have conductivities of $2{\cdot}4 \times 10^{-4}$ (at 25°), $8{\cdot}0 \times 10^{-4}$ (at 25°), 2—3 $\times 10^{-4}$ (at 25°), and $1{\cdot}4 \times 10^{-4}$ (at − 15°) (Sharpe and Emeléus, *J.*, 1948, 2135; Emeléus and Sharpe, *J.* 1949, 2206; Banks, Emeléus, and Woolf, *J.*, 1949, 2861; Fredenhagen and Cadenbach, *Z. anorg. Chem.*, 1929, **178**, 289).

In the liquid state the second group of fluorides, with conductivities below 10^{-4}ohm^{-1} cm.$^{-1}$, do not react at an appreciable rate with alkali fluorides. This group comprises boron trifluoride ($\kappa < 5 \times 10^{-10}$ohm^{-1} cm.$^{-1}$ at −120°), antimony pentafluoride ($\kappa = 1{\cdot}2 \times 10^{-4}$ohm^{-1} cm.$^{-1}$ at 25°], and chlorine trifluoride ($\kappa = 3 \times 10^{-6}$ohm^{-1} cm.$^{-1}$ at 0°; Banks, unpublished).

Reactions which lead to complex-fluoride formation have been demonstrated in bromine trifluoride between compounds containing anions and cations characteristic of the solvent, *e.g.*,

$$K^+BrF_4^- + BrF_2^+SbF_6^- = KSbF_6 + 2BrF_3$$

(Woolf and Emeléus, *J.*, 1949, 2865). These reactions are analogous to neutralization in aqueous solution. It is now found that neutralizations also occur when other members of the first group of fluorides are used as solvent. The conductivity of arsenic trifluoride, for example, is greatly increased by small amounts of potassium or antimonic fluorides, and the compounds KF,AsF_3 and SbF_5,AsF_3 can be isolated from the respective solutions. Equimolecular mixtures of these two compounds in arsenic trifluoride form the complex fluoroantimonate which can be isolated by removal of the solvent *in vacuo*, in agreement with a neutralization equation :

$$K^+AsF_4^- + AsF_2^+SbF_6^- = KSbF_6 + 2AsF_3$$

If no interaction had occurred, a residue of $KAsF_4$ would have remained, since this compound, unlike $SbAsF_5$, is non-volatile *in vacuo*. In addition, although no solid compound could be isolated from boron trifluoride and arsenic trifluoride, the former increased the conductivity of the latter to a small extent and, when it was passed into a solution of potassium fluoride in arsenic trifluoride, potassium tetrafluoroborate was produced. Again, the preparation may be regarded as taking place between potassium tetrafluoroarsenite and an unstable compound $AsF_2^+BF_4^-$ in solution. Similar intermediates have been postulated to explain the formation of hexafluorophosphates in bromine trifluoride solution (Emeléus and Woolf, *J.*, 1950, 164).

Preliminary investigations indicate that iodine pentafluoride behaves in an analogous fashion, since addition of potassium fluoride enhances its conductivity and a compound IF_5,SbF_5 can be prepared in the same manner as the corresponding arsenic compound described above. Finally, although no examples of neutralization reactions in liquid hydrogen fluoride have been reported, it seems probable that potassium hydrogen fluoride would react with the compound $H_2F^+BF_4^-$ (Hantzsch, *Ber.*, 1930, **63**, 1789) in anhydrous hydrogen fluoride to produce potassium fluoroborate.

The structures of the compounds formed between the fluorides of Groups Vb and VIIb require further investigation. The compounds BrF_3,SbF_5, IF_5,SbF_5, AsF_3,SbF_5, $(SbF_5)_2,SbF_5$, and $(SbF_5)_3,SbF_5$ have so far been prepared, but the number of such complexes is, in all probability, not limited to these examples. In particular, the compounds $(SbF_5)_2,SbF_5$ and $(SbF_5)_4,SbF_5$ should be re-examined in view of the present work, since $(SbF_5)_2,SbF_5$ (Ruff and

Plato, *Ber.*, 1904, **37**, 678), for example, may well be a salt $(SbF_3)_2SbF_7$. The anion of this hypothetical salt may be present in the corresponding potassium compound $K_2SbF_7.2H_2O$ (Marignac, *Annalen*, 1868, **145**, 237). It is improbable, however, that all the double fluorides of these groups will be ionic in the solid state, although many may ionise in solution owing to the effect of solvation in altering the type of bonding.

Some observations on viscosities made during the course of this work are of interest. Arsenic trifluoride is about as viscous as water and has a viscosity $\eta = 1{\cdot}17$ centipoises at 8·3°. The plot of log η against the reciprocal of the absolute temperature is linear over the limited range examined (−8° to +10°), and this leads to an activation energy for viscous flow of 2·41 kcals. mole^{-1}, which is approximately a quarter of the latent heat of vaporization of the liquid, 8·57 kcals. mole^{-1} (Russell, Rundle, and Yost, *J. Amer. Chem. Soc.*, 1941, **63**, 2825). This is in agreement with the theory of absolute reaction rates (Kincaid, Eyring, and Stearn, *Chem. Reviews*, 1941, **28**, 301). Antimony pentafluoride in contrast, has a viscosity of 460 centipoises at 20°, which is of the same order as that of glycerol. The temperature variation of the viscosity has not been examined over a sufficiently wide range to decide whether it is an important factor in determining the rapid variation of electrical conductivity with temperature; between 20° and 90° the conductivity increases a hundred-fold, and the corresponding activation energy for the conduction process is 14·3 kcals. mole^{-1}, a value which is considerably higher than the usual values for this quantity. There are, as yet, insufficient data for one to draw any reliable comparison between the physical properties of the corresponding fluorides of Groups Vb and VIIb.

Experimental.

Arsenic Trifluoride.—Moissan observed that arsenic trifluoride was a poor conductor whose conductivity was raised by addition of potassium fluoride. No fluorine was evolved on electrolysis, but the solvent was attacked with the formation of arsenic pentafluoride at the anode, and deposition of arsenic at the cathode, phenomena similar to those observed during the electrolysis of bromine trifluoride.

Arsenic trifluoride was prepared by the action of concentrated sulphuric acid (250 c.c.) on a well-dried, intimate mixture of arsenious oxide (100 g.) and calcium fluoride (120 g.) in a Pyrex-glass apparatus. The product was purified by refluxing it over sodium fluoride and fractionating it through a short Fenske column. It was found, in agreement with Russell, Rundle, and Yost (*loc. cit.*), that specimens so prepared were without action on glass and had a b. p. several degrees lower than that reported by previous workers. The present investigation gave as the b. p. 57·8°/760 mm., a value which altered by 0·03$_5$° per mm. The product had $n_D^{t\cdot4}$ 1·362 and $d_4^t = 2{\cdot}6605 - 0{\cdot}00370t$ in the range 5—25°.

Specific electrical conductivity was measured at 1000 cycles A.C., with an apparatus described by Hasseldine and Woolf (*J. Soc. Chem. Ind.*, in the press). The design of the conductivity cell is shown in the Figure. It consisted of a silica vessel, connected by means of a ground joint to a soft-glass electrode holder which also served to seal the apparatus. The electrodes were of platinum and, when the cell was in use, only a small section of the soft-glass holder was in contact with the liquid under investigation. The arsenic trifluoride, after two distillations from sodium fluoride at atmospheric pressure, had a conductivity of $5{\cdot}29 \times 10^{-6}$ ohm^{-1} cm.$^{-1}$ at 25° and a linear temperature dependence of conductivity ($+1{\cdot}05 \times 10^{-4}$ ohm^{-1} cm.$^{-1}$ deg.$^{-1}$). There was no indication of attack of arsenic trifluoride on the cell, the value of the conductivity remaining constant during 2 hours.

The D.C. resistance was not ohmic, and initially no current flowed below an applied potential of 1·5 v. This value, however, was not reproducible since electrolysis increased the conductivity of the liquid irreversibly; at the end of the experiment the A.C. conductivity had risen to $12{\cdot}9 \times 10^{-4}$ ohm^{-1} cm.$^{-1}$ at 25°.

Two freshly prepared samples of arsenic trifluoride were distilled from sodium fluoride and then twice fractionated *in vacuo*. The middle fractions were vacuum-distilled into the cell. The values obtained for the conductivity are given in Table I. It may be seen that, at 25°, the conductivity of arsenic trifluoride is $2{\cdot}28$—$2{\cdot}30 \times 10^{-6}$ ohm^{-1} cm.$^{-1}$ with a relative temperature coefficient $\left(\frac{1}{\kappa}\frac{d\kappa}{dt}\right)_{25°} = 10\%$.

Table I.

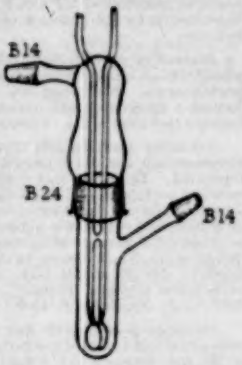
Conductivity of arsenic trifluoride from 0° to 40°.

Specimen I		Specimen II.	
Temp.	$\kappa \times 10^6$, ohm^{-1} cm.$^{-1}$.	Temp.	$\kappa \times 10^6$, ohm^{-1} cm.$^{-1}$.
4·0°	1·83	−0·7°	1·81
11·8	2·01	8·6	2·08
19·6	2·18	14·8	2·22
25·0	2·28	18·9	2·31
29·7	2·40	25·0	2·50
37·8	2·56	29·2	2·61
$d\kappa/dt = 2{\cdot}1_4 \times 10^{-4}$/° c.		$d\kappa/dt = 2{\cdot}6_7 \times 10^{-4}$/° c.	

The kinematic viscosity (ν) of arsenic trifluoride was measured using a modified Ostwald U-tube viscometer with a capillary diameter of 0·60 mm., in accordance with British Standard 188 : 1937. The viscometer was filled directly, and moisture was excluded by means of liquid-air traps. The results are contained in Table II, which also gives values of the dynamic viscosity, $\eta = \nu . d_4$.

Boron Trifluoride.—Commercial boron trifluoride, supplied by courtesy of Imperial Smelting Corporation Ltd., was condensed into the conductivity cell (Fig.) at −120° and a D.C. potential of 110 v. applied. No current was detected with a microammeter, which places an upper limit of 5×10^{-12} ohm^{-1} cm.$^{-1}$ on the conductivity of liquid boron trifluoride.

Conductivity cell.



Antimony Pentafluoride.—Antimony pentafluoride was prepared by passing fluorine over molten antimony trifluoride, previously dried at 120°, and maintained a little above its m. p. (292°) in an electrically heated nickel reaction vessel. The antimony pentafluoride which distilled was purified by vacuum-distillation. The colourless liquid, m. p. 7·0°, was free from tervalent antimony, and was transferred, *in vacuo*, to a soft-glass conductivity cell of a type already described (Greenwood and Emeléus, *J.*, 1950, 987), which was then vacuum-sealed. As the conductivity was below the limit of sensitivity of the A.C. bridge circuits, the current flowing through the cell under an applied D.C. potential of 24 v. was measured by means of a sensitive galvanometer. This procedure was admissible since the resistance was ohmic (Table III), and there was no evidence of any decomposition potential. The specific conductivity of antimony pentafluoride, measured in this way over the range 5—90°, is given in Table IV. The value at room temperature showed no change during one day.

The kinematic viscosity (ν) of antimony pentafluoride was measured, with a British Standard U-tube viscometer with a capillary diameter of 1·15 mm. This viscometer was incorporated in the vacuum-distillation apparatus to facilitate transfer of antimony pentafluoride under anhydrous conditions. After the level of the liquid in the viscometer had been adjusted to the correct height, dry air was admitted through liquid-air traps by a suitable arrangement of taps, and the time of efflux measured. The results so obtained are summarized in Table V. According to Ruff and Plato (*Ber.*, 1904, **37**, 673), antimony pentafluoride has d_4^{20} 2·993. This would give a dynamic viscosity of $\eta \simeq 460$ centipoises at 20°.

TABLE II.

Viscosity of arsenic trifluoride from −5° to +10°.

Temp.	−4·5°	+0·8°	+8·3°
ν, centistokes	0·543	0·500	0·444
η, centipoises	1·15$_5$	1·32$_1$	1·16$_4$

TABLE III.

Current–voltage relation for antimony pentafluoride at 90°.

Volts (v.).	Amps. × 10^6 (I).	$(v/I) \times 10^{-6}$.	Volts.	Amps. × 10^6.	$(v/I) \times 10^{-6}$.
0·3	0·095	3·2	2·4	0·823	2·9
0·6	0·191	3·1	2·8	0·981	2·9
0·9	0·306	2·9	3·25	1·13	2·9
1·2	0·407	3·0	4·0	1·39	2·9
1·6	0·547	2·9	4·5	1·56	2·9
2·0	0·699	2·9	5·5	1·92	3·0

TABLE IV.

D.C. Conductivity of antimony pentafluoride from 5° to 90°.

Temp.	$\kappa \times 10^9$, ohm^{-1} cm.$^{-1}$.	Temp.	$\kappa \times 10^9$, ohm^{-1} cm.$^{-1}$.	Temp.	$\kappa \times 10^9$, ohm^{-1} cm.$^{-1}$.
6·0°	4·37	50·0°	58·5	76·4°	335
17·4	7·65	55·5	105	79·6	395
24·4	11·5	59·8	134	85·6	530
35·5	22·5	65·0	188	89·5	975
45·0	42·6	69·5	251		

TABLE V.

Viscosity of antimony pentafluoride from 0° to 20°.

Temp.	2·2°	13·0°	20·0°
ν, centistokes	246	183	154

Preparation of $KAsF_4$.—In a series of experiments weighed amounts of well-dried potassium fluoride were refluxed with varying amounts of arsenic trifluoride with the exclusion of moisture. Most of the solvent was removed at atmospheric pressure, and the remainder *in vacuo*. The solubility of potassium fluoride was small but complete dissolution of 0·3 g. in 60 c.c. of arsenic trifluoride was obtained after 45 minutes' refluxing. The residue attained constant weight after 5 hours *in vacuo* at room temperature. It was analysed by dissolution in cold sodium hydroxide solution, arsenic being determined iodometrically and fluorine by the Willard–Winter method after distillation from 50% sulphuric acid (Found: As, 39·3; F, 39·1%; equiv., 190. $KAsF_4$ requires As, 39·3; F, 40·0%; equiv., 190). When the potassium fluoride did not dissolve completely the composition of the products varied and they were probably mixtures of KF and $KAsF_4$. The stability of the *compound* was illustrated in some of these experiments by the retention of appreciable quantities of arsenic trifluoride at temperatures up to 100° *in vacuo*.

Preparation of AsF_4SbF_4.—Ruff, Graf, Heller, and Knoch (*Ber.*, 1906, **39**, 4316) observed a white precipitate on mixing arsenic trifluoride with either an equimolecular quantity or an excess of antimony pentafluoride. They suggested that the trifluoride was fluorinated to the pentafluoride which then formed a compound with antimony trifluoride or pentafluoride. It is shown below that the arsenic remains tervalent in a 1 : 1 compound with antimony pentafluoride.

Antimony pentafluoride (2·9 g.) was vacuum-distilled into a silica flask and an approximately equimolecular amount of arsenic trifluoride added (0·68 c.c.). Heat was evolved and a crystalline solid separated. The latter was volatile in a high vacuum, and the bulk of the material in the flask was removed in this way. The solid residue (0·9 g.) was analysed for tervalent antimony and fluorine as described above. In order to determine arsenic and antimony together the former was oxidised to the quinquevalent state with aqueous sodium peroxide and was precipitated and weighed as the pentasulphide after passage of hydrogen sulphide through the solution rendered strongly acid with hydrochloric acid. The antimony in the filtrate was precipitated after dilution and further passage of hydrogen sulphide, the precipitate being converted into the trisulphide by heating it at 280° in a current of oxygen-free nitrogen (Found: As^{III}, 21·1; Sb, 34·8; F, 43·9; Total As, 21·5. AsF_4SbF_4 requires As^{III}, 21·5; Sb, 34·9; F, 43·6; Total As, 21·5%).

Antimony pentafluoride was converted quantitatively into the *compound* AsF_4SbF_4 by treatment with a two-fold excess of the trifluoride. The solid crystallised out at 0° and after evacuation for 2 hours at 30 mm. pressure the weight became constant (Found: As^{III}, 21·3; Sb, 34·3%; equiv., 346. AsF_4SbF_4 requires As^{III}, 21·5; Sb, 34·9%; equiv., 349).

The absence of tervalent and the presence of quinquevalent antimony was shown by qualitative tests with cupferron and rhodamine-B respectively in aqueous solution, thus disposing of the possible structure $AsF_4.SbF_4$.

Complex Formation in Arsenic Trifluoride.—Potassium hexafluoroantimonate. A slight excess of antimony pentafluoride (1·07 moles) was washed into a flask containing potassium fluoride, by means of arsenic trifluoride, and, after refluxing, the excess solvent was removed as previously described. The residue contained only 2% of arsenic and had an equivalent weight of 267 after 2 hours *in vacuo* ($KSbF_6$ = 276). In a second experiment, with a ratio SbF_5/KF of 1·67, the residue contained 0·9% of arsenic.

Potassium tetrafluoroborate. Boron trifluoride was bubbled, in the cold, through 15 c.c. of arsenic trifluoride containing about 0·3 g. of potassium fluoride, and the residue, after partial removal of the solvent at room temperature, was heated to 180° to remove all traces of arsenic trifluoride. This eliminated the necessity of analysing mixtures of $KAsF_4$ and KBF_4. The residue was analysed by precipitating nitron fluoroborate and consisted of KBF_4 80% and KF 20%. The nitron precipitate was identified by analysis (Found: C, 59·9; H, 4·5; N, 14·2. Calc. for $C_{20}H_{17}N_4F_4B$: C, 60·0; H, 4·3; N, 14·0%).

In contrast to this experiment in the presence of arsenic trifluoride, 0·2 g. of potassium fluoride was recovered unchanged after being refluxed at −95° with 20 c.c. of boron trifluoride alone. The condenser was maintained at −112° by means of solid carbon disulphide.

Conductivity of Solutions in Arsenic Trifluoride.—Addition of 0·15 g.-mol. of potassium fluoride per 1000 g. of arsenic trifluoride increased the conductivity of the latter from $2·5 \times 10^{-6}$ to $3·2 \times 10^{-6}$ ohm^{-1} cm.$^{-1}$ at 25°, without all the potassium fluoride going into solution. Similarly 0·135 g.-mol. of antimony pentafluoride per 1000 g. increased the conductivity to $1·03 \times 10^{-4}$ at 25°. The fuming liquid which resulted when boron trifluoride was passed through arsenic trifluoride had a conductivity of $8·4 \times 10^{-4}$ compared with the initial value of $3·7 \times 10^{-6}$ ohm^{-1} cm.$^{-1}$ for the sample of arsenic trifluoride used.

The authors express their gratitude to Professor H. J. Emeléus, F.R.S., for his advice and encouragement, and thank the Department of Scientific and Industrial Research for a Maintenance Grant (A. A. W.) and the Commissioners of the Exhibition of 1851 for the award of an Overseas Studentship (N. N. G.).

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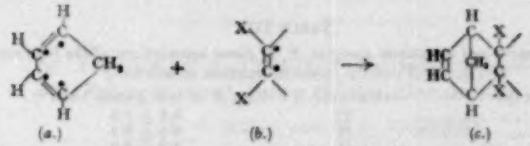
455. *Kinetics of the* cyclo*Pentadiene–Chloranil Reaction. A Note on the Configuration of Transition States in Diene Synthesis.*

By W. Rubin and A. Wassermann.

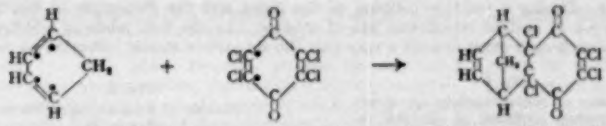
The results of kinetic measurements make it probable that in a reactive collision of Diels–Alder diene associations the diene and the dienophile take up a mutual orientation in which six specified carbon atoms, including the four reactive centres, are not situated in one and the same plane.

In previous papers of this series (Wassermann, *J.*, 1935, 828; 1936, 1028) the kinetics of bimolecular associations of the following general type have been studied, the substituent X being hydrogen in all cases:



(1)

The experiments now to be described deal with the bimolecular addition of *cyclo*pentadiene to chloranil which is formulated as shown below (see Alder, Abderhalden's "Handbuch der Biologischen Arbeitsmethoden," 1933, Abt. I, Teil II, 2. Haelfte Bd. II, p. 3110):



(2)

This diene synthesis is of the same type as (1) but the substituent X is chlorine. It has been found that the kinetic parameters A and the activation energies E of (1) are not markedly different from the corresponding values of (2); and, based on these observations, an attempt is made to draw certain conclusions on the steric configuration of the transition state of these Diels–Alder diene synetheses.

Experimental.—The molar extinction coefficient, β,* of carefully purified chloranil in benzene solution is 15·9 ± 0·3 l. g.-mol.$^{-1}$ cm.$^{-1}$ for light of 4700 A. Beer's law was tested in the range 0·002–0·04 g.-mol./l. (20°) and found to be valid. The rate of (2) is so slow that the light absorption of mixtures of chloranil and *cyclo*pentadiene could be measured before any appreciable formation of the addition product had occurred; and it was established that the addition of *cyclo*pentadiene gives rise to an increase of β. The effect is shown in Fig. 1, the graph relating to a chloranil concentration of 0·0200 g.-mol./l.

Other measurements showed that Beer's law holds for each *cyclo*pentadiene concentration specified in the figure; further, *cyclo*pentadiene–chloranil, the product of (2), is practically colourless, and, therefore, the rate of this diene association can be measured by the same colorimetric technique as that described in our earlier paper (1935, *loc. cit.*). In order to obtain reproducible results, the reaction mixture must be kept in the dark, except during the relatively short periods when light absorption measurements are actually performed. Exposure of mixtures of *cyclo*pentadiene and chloranil for longer times to light of high intensity (*e.g.*, daylight) gives rise to the development of a deep red coloration.

Table I.

Addition of cyclo*pentadiene to chloranil in benzene solution at* 60·0°. (Initial concn. of reactants, 0·0378 g.-mol./l. Thickness of absorption cell, 0·500 cm.)

Time (hours)	0	2·2	5·7	16·2	24·0
Drum reading (Filter S 47)	46·3	54·1	63·7	69·5	81·0 *
k(l. g.-mol.$^{-1}$ hr.$^{-1}$)	—	2·7	3·0	2·8	2·9

* At this stage 70% reaction has taken place.

Typical results of the kinetic measurements are in Table I, and a summary of the experiments is in Table II. The validity of Arrhenius's equation $k = Ae^{-E/RT}$ is shown in Fig. 2; the parameters A

* $\beta = (1/dc) \log_{10} I_0/I$, where d is the thickness of the absorption cell, c the concentration, and I_0 and I are the intensities of the incident and the transmitted light.

and *E* relating to the addition of *cyclo*pentadiene to chloranil are in the first line of Table III, the other figures relating to the previously investigated reactions of the type (1) (Wassermann, *loco. cit.*).

TABLE II.

Addition of cyclopentadiene to chloranil in benzene solution: Summary of kinetic measurements.

Temp.	Initial concn. of reactants (g.-mol./l.). C_5H_6.	$C_6Cl_4O_2$.	k (l. g.-mol.$^{-1}$ hr.$^{-1}$).
10·0°	0·0378	0·0378	0·049 ± 0·005
25·0	0·0378	0·0377	0·25 ± 0·03
	0·0756	0·0189	0·25 ± 0·03
	0·0378	0·0189	0·25 ± 0·03
	0·00940	0·00940	0·30 ± 0·05
40·0°	0·0378	0·0378	0·63 ± 0·1
	0·0189	0·0189	0·73 ± 0·05
60·0	0·0378	0·0378	2·8 ± 0·2

TABLE III.

Kinetic A factors and activation energies, E, of diene associations of the type represented by (1). (All results relate to benzene as solvent.)

Reactant (*b*).	Substituent X.	$\log_{10} A$ (A in l. g.-mol.$^{-1}$ sec.$^{-1}$).	E (kcals.).
Chloranil	Cl	6·2 ± 0·5	14·5 ± 0·5
Benzoquinone	H	6·5 ± 0·4	11·6 ± 0·6
α-Naphthaquinone	H	4·8 ± 0·9	10·0 ± 1·0
*cyclo*Pentadiene–benzoquinone	H	5·5 ± 0·9	13·2 ± 1·0
Acraldehyde	H	6·1 ± 0·3	13·7 ± 0·5
*cyclo*Pentadiene	H	6·1 ± 0·4	16·4 ± 0·6

Discussion.—During a reactive collision of the diene and the dienophile in reactions (1) or (2) two types of mutual orientation are of interest. In the first mode of addition these reactants approach each other in such a way that the six carbon atoms, indicated by asterisks,

FIG. 1.

Influence of cyclopentadiene on molar absorption coefficient of chloranil in benzene (room temp.; 4700 A.).

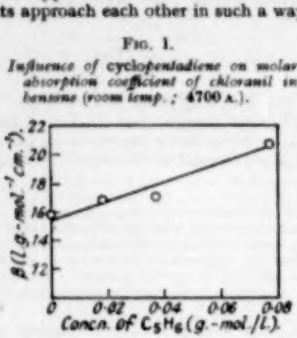
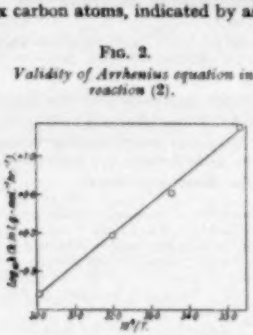


FIG. 2.

Validity of Arrhenius equation in reaction (2).



are situated in one plane, such collisions being conducive for the formation of "planar" transition states. In the alternative type of addition the reactants move towards each other in different planes as schematically represented elsewhere (Wassermann, *J.*, 1935, p. 1512, Fig. 1; *Trans. Faraday Soc.*, 1939, **35**, 841), thereby giving rise to "non-planar" transition states of a steric configuration somewhat similar to that of the fully formed product molecules. In the formation of the planar transition states the required juxtaposition of four carbon atoms can only be brought about if a considerable steric hindrance is overcome, this being due, *inter alia*, to interaction between the diene and the substituent X of the dienophile. Steric effects should be relatively large in reaction (2) because here the atomic radius of X is larger than in the associations of type (1).• If, therefore, planar transition states played a rôle, one would expect that either the non-exponential A factor of the Arrhenius equation or the activation energy, E, or both, would change markedly on passing from the reaction in which X is chlorine to one in which X is hydrogen. It will be seen, however, that all the A factors in col. 3 of Table III agree within the limits of the experimental errors. The activation energies show a moderate variation, and there can be no doubt that the E value of the chloranil reaction is at least 2—3

• The ratio nuclear separation C–Cl/nuclear separation C–H is about 1·6.

kcals. larger than that of the associations involving benzoquinone or α-naphthaquinone; there is no evidence, on the other hand, that the activation energies listed in the last three lines of Table III are smaller than the value in the first line. It appears therefore, that on the whole the activation energy is not fundamentally dependent on the nature of the substituent X. This can be regarded as evidence against the assumption that planar transition states play a rôle in these reactions. The observations are compatible, however, with the alternative mode of addition; for it is obvious from simple considerations of models that steric effects should be less important if the reactants approach each other in different planes, thereby enabling the close proximity of the four reactive centres without considerable interaction between the substituent X and a number of atoms of the diene molecule.

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456. *The Nitration of 2-Hydroxy-4 : 6-dimethylquinoline and the Preparation of Some Related Compounds.*

By J. L. C. MARAIS and O. G. BACKEBERG.

The nitration of 2-hydroxy-4 : 6-dimethylquinoline, first studied by Balaban and reported by him to form the 3-nitro-derivative, has been reinvestigated and found to occur in position 5; in addition, a number of intermediate and related compounds is described.

4 : 6-Dimethyl- and 2 : 4 : 6-trimethyl-quinoline have also been found to be nitrated in position 5.

Acetoacetanilides cannot be cyclised by the action of heat: the product formed is not a quinoline derivative but a symmetrical diphenylurea.

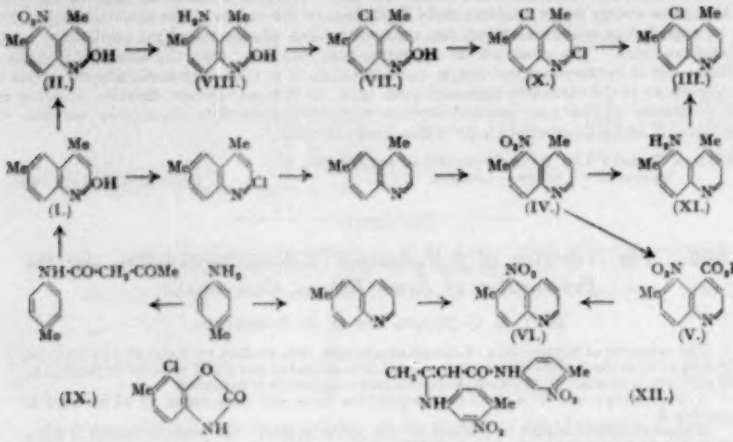
BALABAN (*J.*, 1930, 2346), reporting on the nitration of a number of methyl-substituted 2-hydroxy-4-methylquinolines, stated that nitration occurred in the benzene ring except with the 4 : 6-dimethyl compound (I), where it occurred in position 3.

In general, he determined the orientation of the nitration products by oxidising them to the corresponding benzoxazolones, but he assumed that nitration of the 6-methyl compound had occurred in position 3 because Kaufmann and de Petherd (*Ber.*, 1917, **50**, 336) reported that trinitration of carbostyril formed the 3 : 6 : 8-substitution product, and since he was able to show that nitration had not occurred in position 8, and, because position 6 was occupied, the 3-position was the only one available for substitution. Apart from the fact that the mononitration of (I) and the trinitration of carbostyril are not comparable, it is well known that the heterocyclic ring in quinoline and its derivatives is very resistant to nitration, and a re-investigation of Balaban's nitration product has shown that it is 5-nitro-2-hydroxy-4 : 6-dimethylquinoline.

Attempts to synthesise the 5(or the 7)-nitro-dimethyl compound by cyclisation of 3-nitro-4-methylacetoacetanilide were unsuccessful; when this was warmed on the water-bath with concentrated sulphuric acid, hydrolysis to 3-nitro-4-methylaniline took place, and heating in an inert solvent (cf. Kermack and Muir, *J.*, 1933, 300) afforded *s*-di-(3-nitro-4-methylphenyl)-urea. Kermack and Muir stated that *o*-chloroacetoacetanilide could be cyclised to 8-chloro-2-hydroxylepidine by the action of concentrated sulphuric acid or by heating it in medicinal paraffin at 250°. Repetition of this work showed that, although in the former case cyclisation did take place to some extent (cf. Johnson and Hamilton, *J. Amer. Chem. Soc.*, 1941, **63**, 2867), the product in the latter case was not a quinoline derivative but *s*-di-(*o*-chlorophenyl)urea. It would seem that acetoacetanilides cannot be cyclised by the action of heat but are thereby converted into symmetrical diphenylureas (cf. Leuthardt and Brunner, *Helv. Chim. Acta*, 1947, **30**, 958).

The orientation of Balaban's nitro-compound was determined as follows: (i) 2-Hydroxy-4 : 6-dimethylquinoline (I) was nitrated, and the product converted by the stages shown into 5-chloro-4 : 6-dimethylquinoline (III). (ii) 4 : 6-Dimethylquinoline formed a nitro-derivative, shown to be 5-nitro-4 : 6-dimethylquinoline (IV), which could be converted into the same chloro-quinoline (III). Thus, both the compound (I) and 4 : 6-dimethylquinoline were nitrated in position 5. (iii) On oxidation, the last nitro-compound (IV) formed a carboxylic acid (V) which, on decarboxylation, yielded 5-nitro-6-methylquinoline (VI), previously prepared by Noelting and Trautmann (*Ber.*, 1890, **23**, 3654) and by Bogert and Fisher (*J. Amer. Chem. Soc.*, 1912, **34**, 1569) by nitration of 6-methylquinoline; the former authors determined the orientation of this compound unambiguously.

The nitration of 2 : 4 : 6-trimethylquinoline was also studied: the product proved to be the 5-nitro-derivative. This was established by converting it into the corresponding chloro-



compound, condensing this with phthalic anhydride to the 2-phthalone, and oxidising the latter to the 2-carboxylic acid. On decarboxylation, this acid formed 5-chloro-4 : 6-dimethylquinoline (III).

7-Chloro-6-methylquinoline does not appear to have been previously prepared, and the 8-chloro-isomer was prepared by Mazonski, Mielecki, and Sucharda (*Roczn. Chem.*, 1936, **16**, 519) by a somewhat unusual reaction, *viz.*, by heating *p*-nitrotoluene and glycerol with hydrochloric acid at 160—170°; both these compounds were accordingly prepared, and obtained in good yield, from the corresponding chlorotoluidines by the Skraup reaction as modified by Cohn (*J. Amer. Chem. Soc.*, 1930, **52**, 3685).

Experimental.

(Standardised, short-stem Anschütz thermometers were used for all m. p. determinations.)

5-Nitro-2-hydroxy-4 : 6-dimethylquinoline (II).—This compound was prepared according to Balaban (*loc. cit.*) in 95% yield. It was reduced to the 5-amino-compound (VIII) by tin and glacial acetic acid; from 25 g. of the nitro-compound, after the usual procedure, the amine was obtained as a brown powder (14·4 g.). It crystallised from alcohol in light-brown plates, m. p. 280°; Balaban gives m. p. 264°.

5-Chloro-2-hydroxy-4 : 6-dimethylquinoline (VII).—The foregoing amine (VIII) (15·45 g.) was dissolved with mechanical stirring in hot dilute (1 : 1) hydrochloric acid (235 c.c.) and cooled to 0°; some hydrochloride of the base separated. Sodium nitrite (6·6 g.) in water (16 c.c.) was added in portions, a clear orange-brown solution being obtained. The well-cooled diazotised solution was added dropwise with continuous shaking to a solution of cuprous chloride (from 10·84 g. of copper sulphate) heated on the water-bath, and the heating continued for a further hour. The brown solid which separated was filtered off, washed, and dried; yield 17 g. The *5-chloro*-compound crystallised from dioxan (charcoal) in fine, colourless needles, m. p. 264° (Found: C, 63·8; H, 4·9; N, 6·75. $C_{11}H_{10}ONCl$ requires C, 63·6; H, 4·8; N, 6·7%). Roberts and Turner (*J.*, 1927, 1840) stated that the Sandmeyer method did not give good yields of chloroquinoline derivatives and recommended the Gattermann copper-powder procedure; without exception, the chloro-compounds here described were obtained in excellent yield by the Sandmeyer method.

7-Chloro-6-methylbenzoxazolone (IX).—Attempts to oxidise Balaban's nitro-compound under a variety of conditions to a benzoxazolone derivative led only to the recovery of the unchanged material; when the nitro-group was replaced by chlorine, the resulting compound (VII) was unchanged when subjected to oxidation under the conditions used by Balaban. However, a small yield of a product, which, in the light of the results of this investigation, must have been *7-chloro-6-methylbenzoxazolone* (IX), was obtained under the following conditions. The chloro-compound (VII) (3 g.) was dissolved in aqueous pyridine containing potassium hydroxide (1·25 g.). The solution was boiled under reflux, and potassium permanganate (12·5 g.) added in portions during 30 minutes, boiling being continued for a further hour. The solution was filtered and pyridine removed by steam-distillation; a brown solid separated which crystallised from acetic acid in brown needles (0·2 g.), m. p. 270—280° [Found: C,

52·0; H, 3·3; N, 7·7%; *M* (micro-Rast), 182. $C_9H_6O_2NCl$ requires C, 52·3; H, 3·3; N, 7·6%; *M*, 183·5].

2 : 5-*Dichloro*-4 : 6-*dimethylquinoline* (X).—The 5-chloro-compound (VII) (5 g.) was boiled under reflux with phosphoryl chloride (15 c.c.) for 30 minutes. The bulk of the excess of phosphoryl chloride was removed from the clear solution under diminished pressure, and the residue treated with cold water. The resulting-2 : 5-*dichloro*-compound was filtered off, washed, and dried; yield 5·44 g. It crystallised from alcohol (charcoal) in colourless needles, m. p. 122·5° (Found : N, 6·3. $C_{11}H_9NCl_2$ requires *N*, 6·2%).

2-Chloro-5-nitro-4 : 6-dimethylquinoline was obtained in theoretical yield by the same method from the 5-nitro-compound, and crystallised from alcohol (charcoal) in yellow needles, m. p. 162°; Balaban, using phosphorus pentachloride in addition, got a 32·4% yield and m. p. 157°. The same product was obtained from 2-chloro-4 : 6-dimethylquinoline in 90% yield by the method used by Price, Velzen, and Guthrie (*J. Org. Chem.*, 1947, **12**, 203) for nitration of 2 : 6-dimethylquinoline.

5-*Chloro*-4 : 6-*dimethylquinoline* (III).—The dichloro-compound (X) (2·3 g.) was dissolved in glacial acetic acid (20 c.c.) to which water (1·7 c.c.) had been added. The solution, contained in a reflux apparatus fitted with a mechanical stirrer, was heated in a bath at 70°. Zinc (1 g.; 20-mesh) was added at once, and stirring continued for 6 hours; the solution, which had become cloudy, was decanted from excess of zinc, which was washed with a little acetic acid. The whole was made alkaline with sodium hydroxide and steam-distilled; an oil slowly passed over. The distillate was saturated with salt and extracted with ether, the extract dried (Na_2SO_4), the ether removed, and the residual oil distilled; b. p. 289—290°/624 mm.; m. p. 33·5—34·5°; yield 1·95 g. (Found : C, 69·2; H, 5·3; N, 7·5. $C_{11}H_{10}NCl$ requires C, 68·95; H, 5·2; N, 7·3%). The *picrate* formed fine yellow needles from alcohol, m. p. 219° (Found : N, 13·8. $C_{11}H_{10}NCl,C_6H_3O_7N_3$ requires N, 13·65%); the *styphnate*, glistening yellow needles (from alcohol), m. p. 222° (decomp.) (Found : N, 12·9. $C_{11}H_{10}NCl,C_6H_3O_8N_3$ requires N, 12·8%), and the *mercurichloride*, colourless needles (from dilute hydrochloric acid), m. p. 198—200° (Found : N, 3·0. $C_{11}H_{10}NCl,HgCl_2$ requires N, 3·0%). The above method of reduction gave good yields (*ca.* 90%) when applied to the other 2-chloroquinoline derivatives described later, whereas Mikhailov's method (*J. Gen. Chem. Russia*, 1936, **6**, 511) resulted in hydrolysis to the corresponding 2-hydroxy-compound.

4 : 6-*Dimethylquinoline*.—This compound was prepared in 86·8% yield by reduction of 2-chloro-4 : 6-dimethylquinoline by the method described above. It had b. p. 263—266°/621 mm., m. p. 20·5°; the picrate had m. p. 243°; Manske *et al.* (*Canadian J. Res.*, 1942, **20**, *B*, 133) reported 249°, Ewins and King (*J.*, 1913, **103**, 104) 236—237°, and Knorr (*Annalen*, 1888, **245**, 366) m. p. 230°. The required chloro-compound used in the reduction was obtained in theoretical yield by the action of phosphoryl chloride on the corresponding 2-hydroxy-compound, and had m. p. 95°; Kaslow and Sommer (*J. Amer. Chem. Soc.*, 1946, **68**, 644) reported m. p. 95—96°.

5-*Nitro*-4 : 6-*dimethylquinoline* (IV).—4 : 6-Dimethylquinoline (7 g.), dissolved in concentrated sulphuric acid (35 c.c.), was stirred mechanically and cooled to −5°. A mixture of fuming nitric acid (4·5 c.c.; *d* 1·5) and concentrated sulphuric acid (9 c.c.) was gradually added to the solution, the temperature being kept below 0°. The solution was stirred for a further 30 minutes, poured on ice, and made alkaline with aqueous ammonia; a pale yellow solid (9 g.) separated. It crystallised from high-boiling light petroleum in pale yellow stout rhombs, m. p. 85° (Found : C, 65·6; H, 5·1; N, 13·75. $C_{11}H_{10}O_2N_2$ requires C, 65·35; H, 4·95; N, 13·9%). The *picrate* formed small yellow needles (from alcohol), m. p. 214° (decomp.) (Found : N, 16·4. $C_{11}H_{10}O_2N_2,C_6H_3O_7N_3$ requires N, 16·2%), and the *styphnate*, deep yellow needles (from alcohol), m. p. 231° (decomp.) (Found : N, 15·5. $C_{11}H_{10}O_2N_2,C_6H_3O_8N_3$ requires N, 15·7%).

5-*Amino*-4 : 6-*dimethylquinoline* (XI).—2 G. of the above nitro-compound (IV) were reduced with dilute acetic acid and iron filings according to the method of Noelting and Trautmann (*loc. cit.*), yielding 1·2 g. of pure *amine*, which crystallised from high-boiling light petroleum in stout brown needles, m. p. 97° (Found : N, 16·5. $C_{11}H_{12}N_2$ requires N, 16·3%). The *acetyl* derivative crystallised from water in fine colourless plates as the monohydrate, m. p. 129—130° (Found : N, 12·3; H_2O, 7·5. $C_{13}H_{14}ON_2,H_2O$ requires N, 12·1; H_2O, 7·7%); when dried at 105° for 4 hours it afforded the anhydrous compound, m. p. 147—148°. The amine (XI) was converted into the corresponding 5-chloro-compound (III) previously described, by the Sandmeyer procedure; the free base, its picrate, and styphnate were identical with the compounds obtained from the reduction of 2 : 5-dichloro-4 : 6-dimethylquinoline (X).

5-*Nitro*-6-*methylquinoline*-4-*carboxylic Acid* (V).—The nitro-compound (IV) (2 g.) was added to sodium dichromate (4 g.) in sulphuric acid (3·3 c.c. of concentrated acid in 10 c.c. of water), and the mixture gently heated under reflux for 2 hours; oxidation set in suddenly, with separation of the carboxylic acid. The reaction mixture was poured into water, and the yellow carboxylic acid (0·6 g.) filtered off and purified by dissolution in sodium hydroxide and reprecipitation with acid, had m. p. 266° (decomp.). It was insoluble in the usual organic solvents [Found : C, 57·1; H, 3·7; N, 12·1%; *M* (neutralisation equiv.), 229·1. $C_{11}H_8O_4N_2$ requires C, 56·9; H, 3·45; N, 12·1%; *M*, 232]. The acid was decarboxylated by heating 1 g. in a test-tube over a small flame; the resulting sublimate was extracted with hot dilute hydrochloric acid, and the solution filtered and made alkaline. 5-Nitro-6-methylquinoline (0·2 g.) crystallised from very dilute alcohol (charcoal) in fine yellow needles, m. p. 116—117°, not depressed by admixture with an authentic specimen prepared according to Noelting and Trautmann (*loc. cit.*). The *picrate* formed yellow microcrystalline aggregates (from alcohol), m. p. 194° (Found : N, 16·9. $C_{10}H_8O_2N_2,C_6H_3O_7N_3$ requires N, 16·8%), and the *styphnate*, mustard-coloured needles (from alcohol), m. p. 208° (decomp.) (Found : N, 16·1. $C_{10}H_8O_2N_2,C_6H_3O_8N_3$ requires N, 16·2%).

5-*Chloro*-6-*methylquinoline* was obtained in theoretical yield from the corresponding 5-amino-compound by the Sandmeyer method. It crystallised from dilute alcohol in glistening plates, m. p. 47° (Found : C, 67·7; H, 4·6; N, 7·6. $C_{10}H_8NCl$ requires C, 67·6; H, 4·5; N, 7·9%); the *picrate* was yellow aggregates (from alcohol), m. p. 210° (Found : N, 13·9. $C_{10}H_8NCl,C_6H_3O_7N_3$ requires N, 13·8%);

the *styphnate* found shining yellow needles (from alcohol), m. p. 217° (decomp.) (Found : N, 13·35. $C_{10}H_9NCl.C_6H_3O_8N_3$ requires N, 13·25%).

3-Chloro-4-methylacetoacetanilide was prepared from 3-chloro-4-methylaniline (10 g.) according to Limpach's method (*Ber.*, 1931, **64**, 970) in 88% yield. It crystallised from very dilute alcohol in colourless glistening plates, m. p. 109·5—110° (Found : N, 6·4. $C_{11}H_{12}O_2NCl$ requires N, 6·2%). This compound is mentioned in U.S.P. 2,112,764 but not described.

7-Chloro-2-hydroxy-4 : 6-dimethylquinoline.—3-Chloro-4-methylacetoacetanilide (10 g.) mixed with concentrated sulphuric acid (10 c.c.) was heated on the water-bath for 2 hours. After cooling, the solution was poured into water, and the colourless product (8·9 g.) crystallised from dilute acetic acid in small colourless prisms, m. p. 327° (copper block). As this product was different from the 5-chloro-compound (VII), it could only be the 7-chloro-isomer (Found : C, 63·6; H, 4·9; N, 6·6. $C_{11}H_{10}ONCl$ requires C, 63·6; H, 4·85; N, 6·75%).

2 : 7-Dichloro-4 : 6-dimethylquinoline was obtained in theoretical yield from the foregoing compound by the action of phosphoryl chloride. It crystallised from alcohol in long shining needles, m. p. 139° (Found : N, 6·1. $C_{11}H_9NCl_2$ requires N, 6·2%).

7-Chloro-4 : 6-dimethylquinoline was obtained in 85% yield by reduction of the 2-chloro-compound with zinc and acetic acid. It crystallised from dilute alcohol in long shining needles, m. p. 104° (Found : C, 69·2; H, 5·1; N, 7·2. $C_{11}H_{12}NCl$ requires C, 68·95; H, 5·2; N, 7·3%); the *picrate* formed yellow needles (from alcohol), m. p. 248° (decomp.) (Found : N, 13·8. $C_{11}H_{12}NCl.C_6H_3O_7N_3$ requires N, 13·85%), and the *styphnate* golden-yellow plates (from alcohol), m. p. 244° (decomp.) (Found : N, 13·0. $C_{11}H_{12}NCl.C_6H_3O_8N_3$ requires N, 12·8%).

7-Chloro-6-methylquinoline was obtained in small yield by decarboxylation of the oxidation product from 7-chloro-4 : 6-dimethylquinoline according to the procedure outlined above. It crystallised from dilute alcohol or from high-boiling light petroleum in shining plates, m. p. 77—78° (Found : C, 67·5; H, 4·6; N, 7·7. $C_{10}H_8NCl$ requires C, 67·6; H, 4·5; N, 7·9%). This compound was also prepared from 3-chloro-4-methylaniline by the Skraup reaction as modified by Cohn (*loc. cit.*). The mixture of 5- and 7-chloro-isomers was obtained in 73·5% yield, and fractional crystallisation from high-boiling light petroleum gave pure 7-chloro-compound as the less soluble product; 10 g. of mixed isomers yielded 4·1 g. of pure 7-chloro-compound. The 5-chloro-compound was not isolated in a pure condition from the mother-liquors. The *picrate* of the 7-chloro-compound formed small yellow needles (from alcohol), m. p. 279—280° (decomp.) (Found : N, 13·8. $C_{10}H_8NCl.C_6H_3O_7N_3$ requires N, 13·8%).

2-Chloro-4-methylacetoacetanilide was obtained in 41% yield by the method of Limpach (*loc. cit.*). It crystallised from dilute alcohol in colourless, shining needles, m. p. 90·5° (Found : C, 58·8; H, 5·4; N, 6·4. $C_{11}H_{12}O_2NCl$ requires C, 58·5; H, 5·3; N, 6·2%).

8-Chloro-2-hydroxy-4 : 6-dimethylquinoline.—6 G. of the above acetoacetanilide, on cyclisation with concentrated sulphuric acid as previously described, yielded 0·4 g. of the *quinoline* after crystallisation from alcohol; this formed colourless, shining needles, m. p. 235° (Found : C, 63·7; H, 4·9; N, 6·8. $C_{11}H_{10}ONCl$ requires C, 63·6; H, 4·8; N, 6·75%).

8-Chloro-6-methylquinoline.—Obtained in 58% yield from 2-chloro-4-methylaniline by the Skraup reaction as modified by Cohn (*loc. cit.*), this (b. p. 191—192°/26 mm.) crystallised from high-boiling light petroleum in stout colourless prisms, m. p. 61·5°; the picrate crystallised from alcohol as yellow needles, m. p. 219—220°; Mazonski, Mielecki, and Sucharda (*loc. cit.*) reported 62·5° and 213°, respectively.

Reaction between 3-Nitro-4-methylaniline and Ethyl Acetoacetate.—This reaction was carried out according to (i) Limpach (*loc. cit.*) and (ii) Ainley and King as modified by Carmack (*J. Amer. Chem. Soc.*, 1946, **68**, 1809). (i) From 4 g. of base, prepared according to Ullmann and Dootson (*Ber.*, 1918, **51**, 9), 2 g. of *3-nitro-4-methylacetoacetanilide* were obtained; it crystallised from dilute alcohol in cream-coloured needles, m. p. 84·5° (Found : N, 11·9. $C_{11}H_{12}O_4N_2$ requires N, 11·9%). This compound is mentioned in B.P. 450,021 but not described. (ii) The syrupy reaction product obtained from 46·5 g. of 3-nitro-4-methylaniline, after removal of excess of ethyl acetoacetate, was gently warmed with 200 c.c. of 4% sodium hydroxide and filtered from insoluble material. The filtrate was acidified with dilute hydrochloric acid, and the gummy product which separated solidified in the ice-chest; it was filtered off, washed, and dried, giving 22·5 g. of crude 3-nitro-4-methylacetoacetanilide, m. p. 82·5° after one crystallisation from dilute alcohol. The sodium hydroxide-insoluble material was treated with cold dilute hydrochloric acid, filtered off, washed, and extracted with alcohol, leaving a small quantity of insoluble residue. On evaporation of the alcoholic extract, 14 g. of crude *β-(3-nitro-4-methylanilino)-crotono-3-nitro-4-methylanilide* (XII) were obtained, which crystallised from alcohol in orange-yellow, microcrystalline plates, m. p. 176° (Found : C, 58·3; H, 5·0; N, 15·15. $C_{18}H_{18}O_5N_4$ requires C, 58·4; H, 4·9; N, 15·15%). When this was warmed with dilute hydrochloric acid for one minute, it was hydrolysed to a mixture of 3-nitro-4-methylaniline and the corresponding acetoacetanilide.

The alcohol-insoluble residue referred to above consisted of 0·5 g. of brown solid; it crystallised from dilute acetic acid in pale brown plates, m. p. 256—257° (Found : N, 17·0. Calc. for $C_{11}H_{14}O_4N_4$: N, 17·0%), unaltered by admixture with *s*-di-(3-nitro-4-methylphenyl)urea prepared according to Sonn's method (*Ber.*, 1914, **47**, 2437); m. p.s 251—252° and 245° were reported by Vittenet (*Zentr.*, 1899, **21**, 659) and by Manuelli and Ricca-Rosellini (*Gazzetta*, 1899, **29**, II, 124), respectively.

Attempted Cyclisation of 3-Nitro-4-methylacetoacetanilide.—Warming with concentrated sulphuric acid in the usual manner caused hydrolysis, and only 3-nitro-4-methylaniline was isolated; heating this in an oil-bath at 160—170° for 2 hours, or in medicinal paraffin at 240° for 5 minutes (cf. Kermack and Muir, *loc. cit.*), afforded *s*-di-(3-nitro-4-methylphenyl)urea described above, but no quinoline derivative.

Experiments with o-Chloroacetoacetanilide.—Cyclisation with concentrated sulphuric acid formed 8-chloro-2-hydroxy-4-methylquinoline, m. p. 214·5°, in 26% yield, confirming the result obtained by

Johnson and Hamilton (*loc. cit.*), but, when the acetoacetanilide was heated in medicinal paraffin at 240° for 5 minutes according to Kermack and Muir (*loc. cit.*), the product was not a quinoline derivative, but *s*-di-(*o*-chlorophenyl)urea, m. p. 235·5°, identical with the compound prepared from *o*-chloroaniline by Sonn's method (*loc. cit.*).

5-Nitro-2 : 4 : 6-trimethylquinoline.—2 : 4 : 6-Trimethylquinoline (24 g.), m. p. 45°, on nitration by the procedure described for the preparation of 5-nitro-4 : 6-dimethylquinoline, gave 28·5 g. of the *5-nitro*-compound, which crystallised from dilute alcohol in pale yellow plates, m. p. 84·5° (Found : C, 66·5; H, 5·6; N, 13·0. $C_{12}H_{14}O_2N_2$ requires C, 66·7; H, 5·55; N, 13·0%); the *picrate* crystallised from alcohol as yellow plates, m. p. 175° (Found : N, 15·95. $C_{12}H_{14}O_2N_2,C_6H_3O_7N_3$ requires N, 15·7%). Attempts to convert this nitro-compound into a 2-phthalone led to extensive charring.

5-Amino-2 : 4 : 6-trimethylquinoline was prepared by reduction of the above nitro-compound according to Price *et al.* (*loc. cit.*) in 94% yield. It crystallised from water in small pale yellow needles, m. p. 139—139·5° (Found : N, 15·2. $C_{12}H_{16}N_2$ requires N, 15·05%); the *picrate* formed fine golden-yellow needles, m. p. 227° (decomp.), from alcohol (Found : N, 17·1. $C_{12}H_{16}N_2,C_6H_3O_7N_3$ requires N, 16·9%).

5-Chloro-2 : 4 : 6-trimethylquinoline, prepared in 94% yield from the above amine by Sandmeyer's method as above, crystallised from high-boiling light petroleum in colourless needles, m. p. 49—50°. It was slowly volatile in steam (Found : N, 6·7. $C_{12}H_{14}NCl$ requires N, 6·8%); the *picrate* formed fine yellow needles, m. p. 207°, from alcohol (Found : N, 13·0. $C_{12}H_{14}NCl,C_6H_3O_7N_3$ requires N, 12·9%).

5-Chloro-4 : 6-dimethylquinoline-2-phthalone.—The above 5-chloro-compound (2 g.) was mixed with phthalic anhydride (1·5 g.) and fused zinc chloride (0·2 g.) and heated in an oil-bath at 170—180° for 3 hours. The cooled product was dissolved in acetic acid and poured into water, giving 2 g. of a yellow amorphous solid. This crystallised from dioxan in small dark-yellow needles, m. p. 268° (Found : C, 71·3; H, 4·2; N, 4·4. $C_{20}H_{14}O_2NCl$ requires C, 71·55; H, 4·2; N, 4·2%). On oxidation with nitric acid according to Koenigs and Mengel (*Ber.*, 1904, **37**, 1322), the *phthalone* formed the corresponding 2-carboxylic acid which was insoluble in the usual organic reagents. It was decarboxylated by carefully heating the dry substance in a test-tube; a small quantity of oil was formed which was dissolved in alcohol and converted into the picrate, which after crystallisation from alcohol had m. p. 218°, unchanged by admixture with the picrate of 5-chloro-4 : 6-dimethylquinoline (III).

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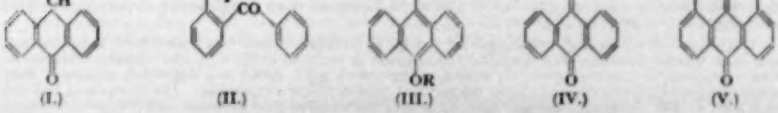
457. *A Molecular Compound of Anthraquinone and Dianthron-9-yl.*

By V. M. INGRAM.

The preparation of a molecular compound, (anthraquinone)$_2$,dianthron-9-yl, is described and its composition established.

DURING attempts to prepare derivatives of 10-diphenylmethyleneanthrone by the condensation of anthrone with the keto-chlorides of aromatic ketones in boiling xylene solution (cf. Schönberg, *et al.*, *J.*, 1946, 442) it was found that dichloro-*m*-nitrodiphenylmethane acted simply as an oxidising agent, the anthrone being converted into dianthron-9-yl (I) • (cf. Ingram, *J.*, 1950, 2246). When the keto-chlorides derived from *o*-benzoylbenzoic acid and its ethyl ester were employed, the product consisted of anthranyl *o*-benzoylbenzoate (II). Attempts to



(I.) (II.) (III.) (IV.) (V.)

condense *o*- and *m*-benzoylbenzoic acid with anthrone by prolonged heating in benzene solution in the presence of piperidine, ammonium acetate, and acetic acid according to Cope's method

• Previously known as 9 : 9′- or 10 : 10′-dianthronyl. The name now used is preferred as being less ambiguous.—ED.

(*J. Amer. Chem. Soc.*, 1941, **63**, 3452) resulted in the formation of a compound consisting of one molecule of dianthron-9-yl combined with two molecules of anthraquinone; the benzoylbenzoic acids take no part in this reaction.

This compound formed pale-yellow prisms, m. p. 241—243° (decomp.), dissolved unchanged in concentrated sulphuric acid, and showed delayed thermochromism in high-boiling solvents; when boiled vigorously for several minutes in methyl salicylate the initially yellow solution slowly became a deep emerald-green but faded to yellow again as the solution cooled. Curiously enough this change was only observed when heating was carried out in small soft-glass (not Pyrex) test-tubes. It appeared likely, therefore, that the thermochromism was not due to the original compound, but to another substance, produced during the heating by dehydration, aerial oxidation, or enolisation induced by the alkali of the glass, or by a combination of these reactions.

The first indications as to the constitution of the compound were obtained by an examination of its behaviour on acetylation and also on oxidation by bromine. When heated first with pyridine and then with acetic anhydride, it gave rise to anthraquinone and an acetyl derivative which could not be isolated in a pure condition, but showed in light-petroleum solution the characteristic mauve fluorescence of 10 : 10′-diacetoxydianthranyl (III; R = Ac).

Treatment of the compound with hot pyridine alone brought about a separation into two fractions, of which the less soluble was identified as anthraquinone, whilst the more soluble fraction gave orange solutions in aqueous alkalis and was oxidised by bromine in pyridine solution to dianthron-9-ylidene(9 : 9′-dianthraquinone) (IV).

From these results it would appear that the substance is a molecular compound of anthraquinone with 10 : 10′-dihydroxydianthranyl (III; R = H) or its keto-form, dianthron-9-yl. Since the original substance has only a very faint colour and does not dissolve in aqueous alkalis until it has been submitted to the enolising action of pyridine, the second component is undoubtedly present in the keto- or dianthronyl form. The relative proportions of the two components were determined by pouring a hot pyridine solution of the compound into an excess of aqueous sodium hydroxide. The weight of anthraquinone thus precipitated corresponded to 45% of that of the original compound. On acidification, the alkaline solution furnished the same amount of 10 : 10′-dihydroxydianthranyl, which was isolated as the diacetyl derivative. The compound therefore contains one molecule of dianthron-9-yl combined with two molecules of anthraquinone.

Confirmatory evidence of the composition was finally provided by the preparation of the compound in quantitative yield by cooling a hot concentrated solution of dianthron-9-yl (1 mol.) and anthraquinone (2 mols.) in a mixture of glacial acetic acid and methyl salicylate.

The peculiar behaviour of the molecular compound in exhibiting delayed thermochromism only when heated in small soft-glass tubes is now readily explicable. The alkali present in the soft glass induces enolisation of the dianthron-9-yl component, and this is followed by aerial oxidation of the resulting 10 : 10′-dihydroxydianthranyl to the thermochromic dianthron-9-ylidene, a process more likely to occur during the vigorous boiling of a small quantity of liquid.

Experimental.

M. p.s are uncorrected. The microanalyses are by Drs. Weiler and Strauss, Oxford.

Preparation of the Molecular Compound.—A mixture of anthrone (5·0 g.), ammonium acetate (4 g.), piperidine (1 c.c.), and glacial acetic acid (6 c.c.) was heated under reflux with benzene (75 c.c.), in an apparatus containing a Dean and Stark water separator, until the melting point of the crystals deposited from a sample of the solution rose to a temperature higher than 210°; this required 30 hours. The *compound* (3·0 g.) separated from glacial acetic acid in arborescent growths of pale greenish-yellow prismatic needles, m. p. 241—243° (decomp.) (Found: C, 83·7; H, 4·3; active H, 0·3. $C_{42}H_{26}O_4$ requires C, 83·8; H, 4·2; active H, 0·25%). It dissolved in concentrated sulphuric acid to form a fluorescent orange solution, from which, after 24 hours at room temperature, it was precipitated unchanged by the addition of ice–water.

Oxidation.—A solution of the compound (0·5 g.) in pyridine (4 c.c.) was boiled for 2 hours, cooled, and then treated dropwise with a solution of bromine in pyridine (16% w/v) until further addition no longer produced a transient green coloration. The yellow solid, which was deposited, separated from acetic acid–methyl salicylate (1 : 1) in magnificent golden-yellow rhomboids. The compound had too high a m. p. [335° (decomp.), copper block] to be used for identification purposes, but it showed the same thermochromic colour changes (emerald green, hot; yellow, cold) in solution as dianthron-9-ylidene (9 : 9′-dianthraquinone), and a microscopic comparison of the highly characteristic crystals with those of an authentic specimen of the quinone left no doubt as to its identity.

Separation of the Compound into its Components.—A pyridine solution (15 c.c.) of the compound (2·0 g.) was boiled for 2 hours and then poured into a well-stirred, aqueous solution of sodium hydroxide (100 c.c.; N.), containing a little sodium sulphite. The anthraquinone thus precipitated was again

heated for half an hour with pyridine (15 c.c.) and reprecipitated with aqueous sodium hydroxide (100 c.c.; N.). It then had m. p. and mixed m. p. 282—283°, and corresponded in amount (0·9 g.) to 90% of that present in the original molecular compound.

The aqueous solution from which the anthraquinone had been separated furnished, on acidification with 5N-hydrochloric acid, 10 : 10'-dihydroxydianthranyl as a pale-yellow precipitate, which after being dried was acetylated by being heated for one hour with pyridine (10 c.c.) and acetic anhydride (2 c.c.). Decomposition with water furnished 10 : 10'-diacetoxydianthranyl (1·1 g.; corresponding to 90% of the original dianthron-9-yl). The diacetyl derivative crystallised from glacial acetic acid (16 c.c.), containing a little acetic anhydride (0·5 c.c.), in needles which showed the characteristic mauve fluorescence in petroleum solution and had m. p. 279—282°, alone and also when mixed with an authentic specimen.

Dianthron-9-ylidene (9 : 9'-*Dianthraquinone*).—For purposes of comparison this compound was prepared according to Barnett and Matthews's method (*J.*, 1923, 380), but purification of the crude product was more rapidly effected by a single crystallisation from acetic acid–methyl salicylate (2 : 1) than by the method described by these authors. It melted with decomposition at 335° when introduced into a copper block at that temperature. Below this point, samples did not melt, but charred completely. Dianthron-9-ylidene exhibits the phenomenon of thermochromism; its solutions are yellow at ordinary temperatures, but become greenish-blue when heated, the colour fading again to yellow as the solution cools.

Solutions of the quinone in acetic acid–methyl salicylate remained unchanged when kept in the dark for a fortnight, but exposure to diffuse daylight at ordinary temperature produced, during the course of a few hours, extensive deposition of small orange needles, which were separated from unchanged dianthron-9-ylidene by being boiled with methyl salicylate. The product did not show thermochromism and was only very sparingly soluble in high-boiling organic solvents, but dissolved readily in sulphuric acid to form dark-red solutions having an intense greenish fluorescence. It does not melt, but chars completely when introduced into a copper block at temperatures above 300°. The constitution has not been determined, but from the results obtained by Schönberg (*loc. cit.*) on the action of sunlight on compounds similar to dianthron-9-ylidene, the substance probably represents a condensed polynuclear *quinone* of type (IV) (Found : C, 87·1; H, 3·25. $C_{28}H_{12}O_2$ requires C, 87·9; H, 3·2%).

Anthranyl o-Benzoylbenzoate (I).—A benzene solution of *o*-benzoylbenzoyl chloride, prepared from the acid (5 g.) and thionyl chloride (Martin, *J. Amer. Chem. Soc.*, 1916, **38**, 1142), was gradually added to anthrone (4·5 g.) dissolved in the same solvent (20 c.c.), the anthrone having previously been enolised by heating for 20 minutes in the presence of pyridine (4 c.c.). The resulting yellow solid consisted of a mixture of anthraquinone, formed by the internal condensation of the acid chloride, and *anthranyl o-benzoylbenzoate*, which, after extraction from the quinone with hot xylene, crystallised from methyl salicylate in colourless hexagonal prisms, m. p. 237—238° (decomp.) (Found : C, 83·4; H, 4·6. $C_{28}H_{18}O_3$ requires C, 83·5; H, 4·5%). The ester was also produced in good yield (74%) in an attempt to prepare 10-(*o*-carbethoxydiphenylmethylene)anthrone by boiling a xylene solution (300 c.c.) of anthrone (17 g.) for 3 hours with the crude keto-chloride prepared from ethyl *o*-benzoylbenzoate (20 g.) and phosphorus pentachloride (20 g.).

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458. *Unsaturated Lactones and Related Substances.* (a) *Introduction.* (b) *Part I. Unsaturated γ-Lactones from Keto-acids. The Position of the Double Bond.*

By F. A. KUEHL, jun., R. P. LINSTEAD, and B. A. ORKIN.

An introduction is given to the series of papers.

Comparative experiments have been carried out on the various reactions used to distinguish between $\alpha\beta$- and $\beta\gamma$-unsaturated γ-lactones. For this purpose $\alpha\beta$- and $\beta\gamma$-angelicalactones and homoangelicalactones have been prepared, and also the lactones of 2-hydroxy*cyclo*hexylideneacetic acid and of 2-hydroxy*cyclo*hex-1-enylacetic acid. Analogous unsaturated lactones containing the *cyclo*pentane ring could not be obtained.

The diagnostic reactions examined were the reducing properties, various colour tests, and the reactions with water, alkali, ammonia, aniline, and alcoholic acid. Of these, clear-cut and reliable differences between the $\alpha\beta$- and $\beta\gamma$-isomerides were shown in the reactions with alcoholic acid and with aniline. The colour reactions and reducing tests are very sensitive to pH and of these the best were the reactions with dichlorophenolindophenol and with ammoniacal silver nitrate.

(a) INTRODUCTION.

IN 1939 a programme of research was commenced on physiologically active unsaturated lactones. This included both a study of naturally occurring material such as the heart poisons of the digitalis group and synthetic studies. The work planned was interrupted by the war and subsequently by other duties. There has been considerable activity in this field during the past decade (see, *e.g.*, review by Haynes, *Quart. Reviews*, 1948, 46) and some of the work carried out by the senior author and his collaborators has been anticipated. The investigation of some

aspects of the chemistry of these interesting materials is now being renewed, and it seems desirable as a first step to give some account of those aspects of our earlier work which are most complete and do not overlap with material published in the interval from other laboratories. This introduction is intended to act as an index to the four papers which follow, and which are necessarily somewhat disconnected.

Part I deals with the preparation of unsaturated lactones from various keto-acids and with reactions which are said to be diagnostic of the position of the double bond (αβ- or βγ-). Part II describes the application of the Rosenmund reaction to the preparation of aldehydo-acids together with certain related topics. Parts III and IV deal with unsaturated lactones which contain a further functional group, either carboxyl or carboxylic ester. Part III describes the lactonisation of β-ketoadipic acid and the chemistry of the substances obtained. Part IV deals with the isomeric materials made by the lactonisation of muconic acid.

The work described in Parts I and II was carried out at Harvard in 1939—1941; that on muconic acid was commenced at Harvard at the same time and is now being continued at the Imperial College. Part III is a description of recent research (1949—1950) at the Imperial College, which is being pursued.

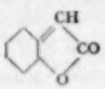
The pharmacological activity of a number of the unsaturated lactones described in these papers has already been reported (Krayer, Mendez, de Espanes, and Linstead, *J. Pharm. Exp. Ther.*, 1942, **74**, 372; Krayer, Mendez, and D. Todd, *ibid.*, 1943, **77**, 113).

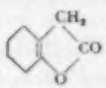
(*b*) Part I.

It was desired to make a direct comparison between pairs of unsaturated γ-lactones with the double bond in the αβ- and βγ-positions. For this purpose there were prepared the two angelicalactones (I and II; R = Me), and the two homoangelicalactones (I and II; R = Et), the preparation of which does not call for special comment. We have also prepared a pair of unsaturated lactones containing the *cyclo*hexane ring (III and IV). Since this work was done (Kuehl, Ph.D. Thesis, Harvard, 1942) the preparation of the αβ-*cyclo*hexane lactone (III) has been described by Cocker and Hornsby (*J.*, 1947, 1157) and by McCrae, Charlesworth, and Alexander (*Canadian J. Res.*, 1943, **21**, *B*, 1), and Newman and Van der Werf (*J. Amer. Chem. Soc.*, 1945, **67**, 233) have described preparations of both of the lactones. In our synthesis, *cyclo*hexanone-2-acetic acid (m. p. 73° in agreement with the above workers, but not with Chuang and Ma, *Ber.*, 1935, **68**, 871, who give m. p. 40°) was prepared from *cyclo*hexanone-2-carboxylic ester by conventional reactions. On direct pyrolysis the keto-acid gave a mixture of αβ- and βγ-unsaturated lactones in which the former predominated. Our results thus resemble those of

(I.)

(II.)


(III.)


(IV.)

Newman and Van der Werf (who used acetic anhydride for the lactonisation) and our products resemble those described in the literature. The solid lactone undoubtedly has the double bond in the αβ-position (see below).

We have also prepared the αβ-lactone by oxidising *cyclo*hexylideneacetic ester with selenium dioxide in acetic anhydride to ethyl 2-acetoxy*cyclo*hexylideneacetate. This on hydrolysis yielded 2-hydroxy*cyclo*hexylidene-1-acetic acid which on pyrolysis yielded the αβ-lactone (III) somewhat contaminated by isomeric impurity.

Comparison between αβ- and βγ-Unsaturated Lactones.—We have applied to these three pairs of lactones the reactions which have been suggested by various workers as being capable of distinguishing between the αβ- and βγ-isomerides, together with a few new diagnostic methods. The reactions examined can be divided into three groups: (i) Colour reactions and reducing properties. (ii) Ring fission by water and alkali. (iii) Ring fission involving the formation of esters and anilides.

The value of the various tests has to be interpreted with caution. It is a matter of difficulty to free the various lactones completely from all traces of their isomerides. Samples of αβ-lactones contaminated with traces of the much more reactive βγ-forms may give quite misleading results in colour and reducing reactions. This difficulty does not apply with the same force to reactions in which stoicheiometric quantities are involved.

(i) The best known colour reaction for unsaturated lactones is the Légal reaction with

nitroprusside. The usefulness of this test as a means for distinguishing between αβ- and βγ-isomerides depends upon careful control of the alkalinity of the solution. The best pH for this purpose is about 11·0 and under the conditions described in the Experimental section a considerable difference between the αβ- and βγ-forms is observable. In our hands the use of potassium ferricyanide as suggested by Linville and Elderfield (*J. Org. Chem.*, 1941, **6**, 273) gave unreliable results. Better than either of the foregoing was 2 : 6-dichlorophenolindophenol which with the βγ-compounds at pH 11 gave a blue fading quickly to a light pink whereas the αβ-compounds gave a permanent blue colour. We also examined the well-known capacity of unsaturated lactones to deposit silver from suitable solutions. We found ammoniacal silver nitrate to give quite distinct differences between αβ- and βγ-compounds whereas Tollens's reagent is immediately reduced by both types.

In general, our observations on these reactions are consistent with the view that the rapid reactions are those of the βγ-compounds, whilst those of the αβ-isomerides may be due to preliminary shift of the double bond to the reactive position, which only occurs readily at higher pH values.

(ii) *Fission by water and alkali.* The αβ-compounds which we examined were neutral in aqueous solution : the development of acidity is a useful indication of the presence of βγ-impurity. Thus, βγ-angelicalactone gave a solution in water of pH 4—4·5. When aqueous solutions of the βγ-compounds were boiled the corresponding γ-keto-acids were slowly formed.

The reactions with alkali are complex and several courses are open according to the experimental conditions. The βγ-compounds are abnormal, being opened rapidly to the salts of hydroxy-acids which are the enolic forms of γ-keto-acids and rearrange into the keto-forms. The αβ-lactones are more normal. They are less acidic and their initial fission is slower. From the alkaline solution obtained it is possible to regenerate some αβ-compound. However, a side reaction intervenes in the migration of the double bond (in either the opened or the unopened lactone) to the βγ-position followed by formation of γ-keto-acid. The extent of this process depends upon the reaction conditions and on the particular system under investigation. A full investigation of these complex reactions calls for refinements in technique which are at present being examined.

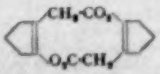
(iii) *Formation of esters and anilides.* None of the αβ-compounds examined reacted with alcoholic hydrogen chloride, whereas all three βγ-compounds were readily converted into the esters of the corresponding γ-keto-acids. These could be readily identified by the formation of ketonic derivatives. Under our experimental conditions normal keto-esters were obtained and not the pseudo-esters recently described by Langlois and Wolff (*J. Amer. Chem. Soc.*, 1948, **70**, 2624).

Lukeš and Prelog (*Coll. Czech. Chem. Comm.*, 1929, **1**, 182, 461, 617) showed that βγ-angelicalactone and homoangelicalactone were converted into the anilides of the corresponding γ-keto-acids by treatment with aniline. We have confirmed this reaction and find it to be useful for diagnosis. All three βγ-compounds give γ-keto-anilides, and none of the αβ-compounds reacts under the same conditions. The structure of the keto-anilides was confirmed by the preparation of ketonic derivatives. We also examined the reaction of ammonia but the results are less clear-cut and the products more difficult to isolate.

The many-sided physiological activity of unsaturated lactones has received much attention recently. The chemical reactivity of βγ-unsaturated γ-lactones is so high that the possibility must be borne in mind that the observed behaviour with biological systems may be due to artefacts and not to the lactones themselves. Results must therefore be interpreted with caution. The chemistry of lactones containing the system $\cdot CH_2\dot{C}\cdot O\cdot CO\cdot$ resembles that of acid anhydrides in many ways and there are analogies with other reactive systems, for example, vinyl ethers and 2 : 3-dihydrofurans.

We can summarise our experience as follows : The most reliable differences between αβ- and βγ-unsaturated lactones are shown by the reactions with alcoholic hydrogen chloride and with aniline. The dichlorophenolindophenol test is a useful colour reaction. The reactivities toward alkali are significantly different but the processes are complex.

(V.)

 (VI.)

Experiments were also made with the object of seeing if an unsaturated lactone could be prepared of similar structure to (III) or (IV) but with a *cyclo*pentane ring in place of *cyclo*hexane.

*cyclo*Pentanone-2-acetic acid, however, behaved differently from the *cyclo*hexane analogue. Direct pyrolysis gave a high-melting substance corresponding to a dimer of the simple lactone (V). This may have the structure (VI). Reaction of *cyclo*pentanone-2-acetic acid with acetic anhydride gave an oil, $C_9H_{12}O_4$, apparently an enol acetate and not an acetoxy-lactone. Pyrolysis of this gave the same dimeric solid. These results are not unexpected; clearly the unsaturated lactone, (V) or a double-bond isomeride, would have a strained and unstable molecule.

Experimental.

1. *Angelicalactones* (I and II; R = Me).—*Preparation.* Wolff's procedure (*Annalen*, 1885, **229**, 249) was used in preference to that of Bredt and of Thiele. The lævulic acid used must be free from its ethyl ester. The method of purification of the lactones used by Wolff is unnecessarily complex; it is sufficient to distil the crude lactonic product twice through a good column. 52 G. of acid yielded 17—20 g. of $\beta\gamma$-lactone and 3—5 g. of $\alpha\beta$-lactone. More $\alpha\beta$-lactone could be prepared by isomerising the $\beta\gamma$-lactone by the method of Thiele, Tischbein, and Lossow (*ibid.*, 1901, **319**, 180). The physical properties of the two lactones were :

	B. p./760 mm.	B. p./mm.	M. p.	n_D^{20}.	d_4^{20}.	$[R_L]_D$.
$\alpha\beta$-	209°	73°/3	< −80°	1·4454	1·081	24·64
$\beta\gamma$-	167	53°/12	+18	1·4476	1·091	24·04

Colour reactions. Standard solutions were prepared from 20 mg. of each lactone and 4 c.c. of 50% alcohol. One c.c. of this solution was added to an equal volume of freshly prepared aqueous sodium nitroprusside. ½ C.c. of this mixture was then added to 2 c.c. of each of the following solutions: 1% disodium hydrogen phosphate, 2% borax, 1% sodium carbonate, 1% sodium hydroxide, the pH's being 8, 9, 11, and 13, respectively. The following colours were observed :

pH.....	8.	9.	11.	13.
$\alpha\beta$-Lactone	Nil	Nil	Pink, fading fast	Immediate red, fading in 30 secs.
$\beta\gamma$-Lactone	Nil	Light pink, becoming stronger	Immediate dark red, fading slowly	Bright red, fading in 30 secs.

Similar tests were carried out with a 0·1% solution of 2 : 6-dichlorophenolindophenol in place of the nitroprusside, the resulting mixture being added to the buffer solutions.

pH	8.	9.	11.	13.
$\alpha\beta$-Lactone ...	No change	No change	Slow fading	Fades rapidly through green to colourless
$\beta\gamma$-Lactone ...	Fades to brownish-red	Fades rapidly to brownish-red	Fades very rapidly to brownish-red	Fades instantaneously to brownish-red

Both lactones gave negative Schiff reactions and immediate deposition of silver from Tollens's reagent. Ammoniacal silver nitrate (prepared by adding ammonia dropwise to 10% silver nitrate until the precipitate just redissolved) was unaffected by the $\alpha\beta$-lactone and gave an instantaneous precipitate of grey-black silver with the $\beta\gamma$-lactone.

Reactions with alcohol. $\alpha\beta$-Angelicalactone (2·9 g.) was refluxed with 50 c.c. of 95% alcohol, 2 c.c. of 10% hydrochloric acid, and 6 c.c. of water (1 hour). The bulk of the alcohol was removed, and the residue taken up in ether and extracted with concentrated potassium carbonate solution and with water. The residue after removal of the solvent was distilled, the $\alpha\beta$-lactone being recovered, b. p. 45°/1 mm., neutral in aqueous solution, reducing Tollens's reagent but not ammoniacal silver nitrate, and giving no ketonic derivatives.

A similar experiment was carried out with 2·75 g. of $\beta\gamma$-angelicalactone. The neutral product (1·7 g.) distilled at 67°/3 mm. and gave the semicarbazone of ethyl lævulate, m. p. and mixed m. p. 148—149°.

Reactions with aniline. $\beta\gamma$-Angelicalactone (1·01 g.) was set aside with freshly distilled aniline (1·12 g.). After 24 hours the solid product was triturated with hexane, dried on a tile, and crystallised from hexane. The lævulic anilide obtained melted at 99—100° and gave a *semicarbazone*, m. p. 172° (Found: C, 58·0, 58·2; H, 6·6, 6·5; N, 24·2, 23·9. $C_{12}H_{15}O_2N_3$ requires C, 58·1; H, 6·5; N, 22·6%), and a 2 : 4-dinitrophenylhydrazone, m. p. 224°. The anilide is identical with that described by Lukeš and Prelog (*loc. cit.*) and by Helberger *et al.* (*Annalen*, 1949, **561**, 215). The ready formation of ketonic derivatives confirms the open-chain keto-formula assigned by Lukeš and Prelog.

A corresponding experiment with the $\alpha\beta$-lactone left a clear liquid after 4 days. From this, unchanged aniline and $\alpha\beta$-lactone were recovered.

2. *Homoangelicalactones* (I and II; R = Et).—Methyl homolævulate was prepared following Clutterbuck and Raper (*Biochem. J.*, 1925, **19**, 292) from β-carbethoxypropionyl chloride and ethylzinc iodide. On hydrolysis it gave homolævulic acid, m. p. 39—40° (Maire, *Bull. Soc. chim.*, 1908, **3**, 285, gives m. p. 36—37°). The yield was 66 g. of keto-acid from 100 g. of the half-chloride. The semicarbazone melted at 169—170° (Campbell and Thorpe, *J.*, 1910, **97**, 1315, give m. p. 176°). The keto-acid (66 g.) was kept for 3 hours with acetic anhydride (68 g.) and a few drops of acetyl chloride. The low-boiling product was distilled out at 60°/10 mm., and the residual acetoxy-lactone pyrolysed at about 200°/200 mm. The combined crude unsaturated lactone was washed in ethereal solution with aqueous

sodium hydrogen carbonate and distilled. The *βγ*-homoangelicalactone obtained boiled steadily at 49°/1·5 mm. and had n_D^{20} 1·4548; d_4^{20} 1·0662 (Found: C, 63·9; H, 7·3. Calc. for $C_9H_{14}O_2$: C, 64·25; H, 7·1%); yield, 57%. The *αβ*-isomeride was prepared by heating the *βγ*-lactone (26 g.) for 2 hours on the steam-bath with a few drops of triethylamine. The product was distilled, and the low fraction again treated with triethylamine. The united high fractions gave 15 g. of the *αβ*-homoangelicalactone, b. p. 72°/1·5 mm., n_D^{20} 1·4576, d_4^{20} 1·0704 (Found: C, 63·9; H, 7·3%).

The colour reactions were carried out as for the lower homologues:

Sodium nitroprusside:

At pH.....	8.	9.	11.	13.
αβ-Lactone ...	No change	Faint pink	Pink	Strong red, changing to yellow
βγ-Lactone ...	Faint pink	Pink	Strong red, fading in 1 min.	Intense red, changing rapidly to yellow.

2 : 6-Dichlorophenolindophenol:

At pH.....	8.	9.	11.	13.
αβ-Lactone ...	← No change in 5 minutes →			Fades to brown in 10 secs.
βγ-Lactone ...	Fades in 5 secs.	Fades in 3 secs.	Fades immediately to brown	

	Tollens's reagent:	Ammoniacal silver nitrate:
αβ-Lactone ...	Grey, turning to black in 5 secs.	No colour or precipitate in 5 mins.
βγ-Lactone ...	Immediate black precipitate	Black precipitate in 1 sec.

βγ-Homoangelicalactone was refluxed with alcoholic hydrogen chloride as described for the lower homologue. The neutral product boiled at 62—63°/1 mm., had n_D^{20} 1·4235 and no reducing properties. It yielded the semicarbazone of ethyl homolævulate, m. p. and mixed m. p. 106—107°. When the *αβ*-lactone was treated similarly it was substantially unchanged, with b. p. 66·5—67°/1 mm. and the reducing properties described above.

When *βγ*-homoangelicalactone was left overnight with aniline (1 mol.) it formed a white solid which on crystallisation from benzene–hexane gave beautiful crystals of homolævulic anilide, m. p. 91—92°, in agreement with Lukeš and Prelog (*loc. cit.*). The *semicarbazone* formed plates, m. p. 161—162°, from 50% alcohol (Found: C, 59·9, 59·9; H, 7·0, 6·9; N, 21·9, 21·7. $C_{10}H_{19}O_3N_3$ requires C, 59·5; H, 6·9; N, 21·4%). Under the same conditions the *αβ*-lactone did not deposit any solid and was recovered unchanged.

3. *Lactones of* 2-*Hydroxy*cyclo*hexylideneacetic Acid and of* 2-*Hydroxy*cyclo*hex*-1-*enylacetic Acid* (III and IV).—"Molecular" sodium (22·9 g.) in dry benzene (850 c.c.) was treated with ethyl *cyclo*hexanone-2-carboxylate (170 g.). After 2½ hours' stirring on the steam-bath, ethyl chloroacetate (135 g.) was added in drops and the product heated overnight. Distillation of the neutral product yielded 127 g. (49%) of diethyl *cyclo*hexanone-2-carboxylate-2-acetate, b. p. 185—195°/25 mm. Hydrolysis of this (2 vols. of concentrated hydrochloric acid; 8 hours' refluxing) and fractionation of the product yielded 46·5 g. (60%) of *cyclo*hexanone-2-acetic acid, b. p. 147—152°/2 mm., together with a small forerun of unsaturated lactone (7·5 g.). After dissolution in alkali, followed by acidification, ether extraction, and distillation, the *cyclo*hexanone-2-acetic acid could be crystallised from benzene–hexane; it had m. p. 72·5—74° (Found: C, 61·4; H, 7·8%; equiv., 154·0, 156·1. Calc. for $C_8H_{14}O_3$: C, 61·5; H, 7·7%; equiv., 156·1). The semicarbazone of the acid melted at 134—135° and its ethyl ester at 195—196° (Chuang and Ma, *loc. cit.*, give 191—193°). Preparation of the acid from sodamide, *cyclo*hexanone, and ethyl chloroacetate was less satisfactory but gave the same product.

Lactonisation. The solid keto-acid (46·5 g.) was heated at 280° for one hour, and the residue distilled through a column. The yield of crude lactone (b. p. 105—115°/1 mm.) was 73%. Further fractionation yielded the *αβ*-lactone (III), b. p. 108—108·5°/1 mm. (42%), which could be further purified by crystallisation from ether at −50°. It then melted at 34° (Found: C, 69·4; H, 7·4. Calc. for $C_8H_{12}O_2$: C, 69·5; H, 7·2%). The equivalent, determined by addition of excess of alkali and back titration, was 141·8 (Calc.: 138·1); n_D^{21} 1·5094; d_4^{21} 1·1245, whence $[R_L]_D$ 36·69, an exaltation of 0·76 unit.

A less satisfactory method of preparation is the following: ethyl *cyclo*hexylideneacetate (29 g.) was refluxed with 60 c.c. of acetic anhydride and 20 g. (1 mole) of selenium dioxide for 2½ hours. The product was cooled and filtered; the filtrate was warmed with water, neutralised with sodium hydrogen carbonate, and extracted with ether. The ethereal solution (Norite) was dried and freed from solvent, and the residue distilled. Ethyl 2-acetoxy*cyclo*hexylideneacetate distilled at 102—106°/2·5 mm. (25% yield). It was hydrolysed with 25% aqueous sodium hydroxide at room temperature. The 2-*hydroxy*cyclo*hexylideneacetic acid* produced had m. p. 154° (Found: C, 61·6; H, 7·7%; equiv., 158·5. $C_8H_{12}O_3$ requires C, 61·5; H, 7·8%; equiv., 156·1). It was heated at 240° for 15 minutes and the product separated into acid and pseudo-acid fractions. The acid fraction was again pyrolysed, and the united pseudo-acid fractions were distilled. The *αβ*-lactone (III), isolated in this way, resembled that already described in reducing properties, b. p. (127—133°/9 mm.), and refractive index (n_D^{20}, 1·5106). The m. p. was low (5—10°), and the mixed m. p. intermediate (14—20°) (Found: C, 69·4; H, 7·2. Calc. for $C_8H_{12}O_2$: C, 69·5; H, 7·2%).

To obtain the *βγ*-lactone (IV) the *αβ*-isomeride was repeatedly distilled at atmospheric pressure through a column. The low-boiling fraction was accumulated and distilled at 1 mm. The fraction

of b. p. 88—93°/1 mm. gave the keto-anilide (see below) in 95% yield and hence must have been substantially pure; it could not be obtained crystalline (Found: C, 69·1; H, 7·6%).

Reactions. These were carried out as described for previous lactones.

Sodium nitroprusside:

pH	8.	9.	11.	13.
αβ-Lactone ...	←	No colour change	→	Yellow colour
βγ-Lactone ...	← Faint pink →		Strong red, fading in 2 mins.	Strong red, fading to yellow in 30 secs.

A positive Légal reaction was given by the αβ-lactone in higher concentrations.

2 : 6-Dichlorophenolindophenol:

pH	8.	9.	11.	13.
αβ-Lactone ...	←	No colour change	→	Colour faded in 30 secs.
βγ-Lactone ...	Colour faded to brown in 1 min.		Colour faded immediately	Colour faded immediately

The βγ-lactone gave an immediate black precipitate with Tollens's reagent and with ammoniacal silver nitrate. The αβ-lactone gave a positive Tollens's test in 2 seconds but no reaction with ammoniacal silver nitrate in 3 hours.

The αβ-lactone was substantially unchanged by boiling with water for 8 hours; the βγ-lactone gave 10% of keto-acid under these conditions. A solution of the αβ-lactone in 20% aqueous sodium hydroxide was kept overnight; the pseudo-acid fraction (38%) was unchanged lactone, the acid fraction (62%) was *cyclo*hexanone-2-acetic acid (m. p. and mixed m. p.).

The βγ-lactone was boiled for 1 hour with alcoholic hydrochloric acid as already described. No lactone could be detected in the product, which was identified as ethyl *cyclo*hexanone-2-acetate by the formation of the semicarbazone; m. p. and mixed m. p. 195—196°. The αβ-lactone was unchanged under these conditions.

The βγ-lactone was kept for 2 days at room temperature with aniline. The solid product was triturated with ether and crystallised from benzene–hexane. The ***anilide*** (95%) of *cyclo*hexanone-2-acetic acid had m. p. 119·2—120° (Found: C, 73·1; H, 7·3. $C_{14}H_{17}O_2N$ requires C, 72·7; H, 7·4%), and formed a ***semicarbazone***, m. p. 196·5—197° (Found: C, 62·5; H, 6·9. $C_{10}H_{20}O_3N_4$ requires C, 62·5; 6·9%). A similar experiment with the αβ-isomeride gave unchanged starting materials.

4. *Attempted Preparation of Unsaturated Lactone from* cyclo***Pentanone-2-acetic Acid.***—*cyclo*Penantone-2-acetic acid (Linstead and Meade, *J.*, 1934, 940) was pyrolysed in 10-g. lots at 270° for 1 hour, during which time about 1 c.c. of water distilled out. Heating of the product at 20 mm. left the bulk behind as an intractable tar, and an indefinite distillate passed over of which a considerable portion boiled at 119°. Trituration of the distillate with ether left a crystalline solid. The ether-soluble portion yielded no lactonic product. The solid crystallised from benzene–hexane and melted at 169·5—171·5° and was probably the dimeric ester (VI) (Found: C, 67·6; H, 6·5%; *M* (Rast), 252; equiv., 120·7. $C_{14}H_{14}O_4$ requires C, 67·7; H, 6·6%; *M*, 248; equiv., 124). No reactions typical of unsaturated lactones were given by this solid or by the liquid portion of the distillate.

*cyclo*Pentanone-2-acetic acid (5 g.) was heated for 30 minutes with acetic anhydride (4 g.) and two drops of acetyl chloride. The bulk of the acetic acid and anhydride was then removed by distillation, and the residue warmed with water and extracted by means of ether. Distillation yielded an oil, b. p. 111·5°/2·5 mm., apparently ***2-acetoxycyclopent-1-enylacetic acid*** (Found: C, 58·5, 58·4; H, 6·6, 6·7. $C_9H_{12}O_4$ requires C, 58·7; H, 6·6%). The material was unsaturated, did not form a semicarbazone, and regenerated the parent keto-acid on alkaline hydrolysis. On pyrolysis, in an atmosphere of nitrogen, the enol acetate (25 g.) began to lose acetic acid at about 180°. Distillation of the product at 3 mm. yielded material of indefinite b. p. which was soluble in aqueous alkali, and gave a positive Légal but a negative Tollens reaction. The highest-boiling portion yielded some of the dimeride $C_{14}H_{18}O_4$, m. p. 170°, described above. The remainder of the material appeared to be essentially a mixture of *cyclo*pentanone-2-acetic acid and the unchanged enol acetate, and we obtained no reliable evidence of the presence of unsaturated lactone in it.

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459. *Unsaturated Lactones and Related Substances. Part II. The Synthesis of Aldehydo-acids by the Rosenmund Reaction.*

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The Rosenmund method for the preparation of aldehydes can be applied to the synthesis of the half-aldehydes of succinic acids. *cyclo*Hexylsuccinic acid gives an inseparable mixture of the two isomeric half-esters which, through the acid chlorides, yields a mixture of the two corresponding aldehydo-esters (α- and β-*cyclo*hexyl-β-formylpropionic ester) which are easily separated through the semicarbazones. The α-*cyclo*hexyl derivative has been independently synthesised from the product of the formylation of *cyclo*hexylsuccinic ester. The β-*cyclo*hexyl derivative is identical with that made by Elderfield and his co-workers by another method. The formylation of an α-substituted succinic ester thus occurs on the unsubstituted carbon atom, contrary to Ranganathan and in agreement with Carrière.

THE most important cardiac glycosides, such as those of *digitalis*, contain a characteristic unsaturated γ-lactone group substituted by a steroid residue on the β-carbon but with no γ-substituent. This lactone is formally derived by loss of water from the enolic form of a β-aldehydo-acid. With the object of extending our knowledge of these comparatively inaccessible compounds, we have investigated the partial reduction of succinic acids.

It has been shown (Rosenmund, *Ber.*, 1918, **51**, 585; Rosenmund and Zetzsche, *ibid.*, p. 594; Rosenmund and Zetzsche, *ibid.*, 1921, **54**, 425; Zetzsche and Flütsch, *ibid.*, p. 2888; Zetzsche and Enderlin, *ibid.*, 1922, **55**, 609) that acid chlorides can be hydrogenated to aldehydes in the presence of a poisoned palladium catalyst, and that the reaction can be used for the preparation of the dialdehydes of dibasic acids (Zetzsche and Flütsch, *loc. cit.*; Zetsche and Enderlin, *loc. cit.*). We now find that it can be successfully used for the preparation of the corresponding half-aldehydes.

The half-methyl ester, half-chloride of succinic acid yielded succinaldehydic ester in 60% yield.* The product was characterised as the semicarbazone, which was hydrolysed to the known semicarbazone of succinaldehydic acid.

Attention was next turned to the *cyclo*hexylsuccinic acid series in which the alicyclic ring parallels ring D of the steroid skeleton. The parent acid (I) was readily prepared by the interaction of *cyclo*hexyl bromide with the sodium derivative of carbethoxysuccinic ester, followed by hydrolysis. It was hoped that the large unsymmetrical substituent would bring about some distinction between the two carboxyl groups in their ease of esterification (compare Bone, Sudborough, and Sprankling, *J.*, 1904, **85**, 534). The addition of sodium methoxide to the anhydride of (I), however, gave a liquid mixture of the half-esters (II; R = H) and (III; R = H) which could not be separated.

$$\underset{\text{(I.)}}{C_6H_{11}\cdot\underset{CO_2H}{\underset{|}{C}}H\cdot CH_2\cdot CO_2H} \longrightarrow \underset{\text{(II.)}}{C_6H_{11}\cdot\underset{CO_2Me}{\underset{|}{C}}H\cdot CH_2\cdot COR} + \underset{\text{(III.)}}{C_6H_{11}\cdot\underset{COR}{\underset{|}{C}}H\cdot CH_2\cdot CO_2Me}$$

By the addition of sodium benzyloxide to the anhydride of (I), it was found possible to isolate one of the half benzyl esters as a homogeneous crystalline solid, but in too poor yield for practical purposes. At the time that this work was done (1941), it was not known that the half-esters half-chlorides of unsymmetrically substituted succinic acids could rearrange in the manner which has since been demonstrated by Cason (*J. Amer. Chem. Soc.*, 1947, **69**, 1548) and Ställberg-Stenhagen (*ibid.*, p. 2568). The half methyl esters were accordingly converted into the mixture of half-ester half-chlorides (II and III; R = Cl). This again resisted all attempts at separation of the isomerides. There was no selective decomposition of the two acid chloride groups with either alkalis or *p*-toluidine. In the course of this phase of the work,

$$\underset{CO_2R}{\underset{|}{C}}H\cdot CH_2\cdot CO\cdot NH\cdot C_7H_7 \quad \text{(IV.)}$$

which is described in detail in the experimental section, the *p*-tolylimide and di-*p*-toluidide of (I) were prepared, and a homogeneous mono-*p*-toluidide (probably IV; R = H) was obtained by the action of *p*-toluidine on the anhydride: it yielded a homogeneous methyl ester.

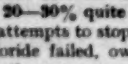
In view of these difficulties we examined the Rosenmund reduction of the mixed half-ester half-chloride (II and III; R = Cl), in the hope that the separation of the two aldehydo-esters would be simpler. These expectations were realised.

The hydrogenation required a catalyst containing only a trace of the usual sulphur-

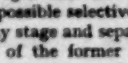
* We are indebted to Dr. James Cason for this experiment.

quinoline poison; if the customary amount of poison was added, absolutely no reduction occurred. About half the theoretical amount of hydrogen chloride was liberated rapidly, and a further 20—30% quite slowly. This suggested a possible selective reduction of the two chlorides but attempts to stop the reaction at the half-way stage and separate the aldehyde and unreacted chloride failed, owing to the polymerisation of the former during fractional distillation. For the same reason it was found desirable to carry the reaction to completion, distil the aldehyde rapidly under reduced pressure and convert it at once into semicarbazone. The yield of semicarbazone (V and VI) is 90% and the overall yield in the 6-stage synthesis from *cyclo*hexylcarbethoxysuccinic ester is over 50%.

The semicarbazone had an indefinite melting point but was easily separated into two isomeric components, melting at 151° and 118—119°. These substances undoubtedly have the structures (V) and (VI), respectively.



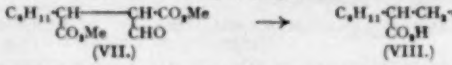
(V.), m. p. 151°



(VI.), m. p. 118—119°

While this work was in progress Elderfield and his co-workers described some related syntheses (Fried, Rubin, Paist, and Elderfield, *Science*, **1940**, **91**, 435; Rubin, Paist, and Elderfield, *J. Org. Chem.*, **1941**, **6**, 260; Paist, Blout, Uhle, and Elderfield, *ibid.*, p. 273). In the course of this they prepared the ester-semicarbazone (VI) by a method which left little doubt as to the structure. Through the kindness of Professor R. C. Elderfield we have compared the derivatives formed by the two methods. Elderfield's compound melted at 119—119·5° and a direct comparison proved its identity with ours.

The structure of the second isomeride was proved as follows: the dimethyl ester of *cyclo*hexylsuccinic acid was formylated by means of ethyl formate and sodium ethoxide, following the general method of Wislicenus, Böklen, and Reuthe (*Annalen*, **1908**, **363**, 340). The product gave every indication of being a mixture of the true formyl ester (VII) and its enolic isomeride. Hydrolysis and decarboxylation of (VII) to the desired aldehydo-acid proved difficult, as is generally true for substances of this class (Carrière, *Ann. Chim.*, **1922**, **17**, 38; Ranganathan, *J. Indian Chem. Soc.*, **1939**, **16**, 107). The best results were obtained by using aqueous oxalic acid at 100°. The aldehydo-acid (VIII) [which may exist wholly or partly in the lactol form (Carrière, *loc. cit.*; Blaise and Courtot, *Bull. Soc. chim.*, **1906**, **35**, 989)] yielded a semicarbazone of m. p. 175°. This on treatment with diazomethane gave the semicarbazone of the corresponding methyl ester (V), m. p. 150°. This was identical with the high-melting isomeride from the Rosenmund reaction. The identity was confirmed by the preparation from both samples of the semicarbazone of the same 2 : 4-dinitrophenylhydrazone.



(VII.) (VIII.)

This work proves that the formylation of the ester of a monosubstituted succinic acid (such as I) occurs on the methylene group. This was assumed by Carrière (*loc. cit.*) in his investigation of the corresponding derivatives of ethylsuccinic acid and is clearly to be expected on general grounds. Ranganathan (*loc. cit.*) has, however, taken the opposite view. He investigated the formylation of *cyclo*pentylsuccinic ester and interpreted the reaction as proceeding on the substituted carbon atom, so that the final product would be β-formyl-β-*cyclo*pentylpropionic acid (type VI and not type V). The present work shows this view to be mistaken, and the structural formulæ proposed by Ranganathan require correction in this respect. Ranganathan also carried out some preliminary experiments in the *cyclo*hexane series but does not appear to have proceeded beyond the anhydride of the parent acid (I). Since this work was completed Swain, Todd, and Waring (*J.*, **1944**, 548) have described the formylation of *cyclo*hexylsuccinic ester and have given the products the structures (VII) and (VIII) by analogy with the formylation of phenylsuccinic ester. These structures are now proved.

Only preliminary work was possible on the lactonisation of the aldehydo-acids described in this paper, but similar studies have been described by Elderfield, Todd, and their collaborators (*locc. cit.*).

Experimental.

(All m. p.s are corrected.)

Methyl β-Formylpropionate.—Succinic half methyl ester acid chloride was prepared by the action of phosphorus oxychloride on the sodium salt (Michaelis and Hermens, *Ber.*, **1892**, **25**, 2747). The latter compound was prepared by the action of sodium methoxide on succinic anhydride as in the case

of the *cyclo*hexyl analogue described below. The acid chloride (12·7 g.), b. p. 84—85°/14—15 mm., in 50 c.c. of xylene was reduced in the presence of 2 g. of palladium–barium sulphate catalyst and 40 mg. of sulphur–quinoline poison. The reaction was conducted at 110° (bath temp.) with vigorous agitation (Hershberg stirrer) according to Cason and Hershberg (*Org. Synth.*, **21**, 87). After 90% of the hydrogen chloride had been liberated (2½ hours) the mixture was cooled, treated with charcoal, filtered, and distilled. The aldehyde (5·9 g.) boiled at 69—70°/14 mm. It reduced Tollens's reagent and Fehling's solution, formed a bisulphite addition compound, and yielded the *semicarbazone* of methyl β-formylpropionate, which formed large colourless prisms, m. p. 130—131°, from methanol (Found: C, 41·3; H, 6·2. $C_6H_{11}O_3N_3$ requires C, 41·6; H, 6·4%).

When the semicarbazone was suspended in N-sodium hydroxide solution it gradually went into solution and the semicarbazone of the corresponding acid was precipitated on the addition of mineral acid. This compound crystallised in small, well defined, colourless prisms, m. p. 190—191° (decomp.) (Carrière, *loc. cit.*, gives m. p. 194—195°).

1 : 1 : 2-*Tricarbethoxy*-1-*cyclo*hexylethane.—The sodium salt of carbethoxysuccinic ester was prepared by adding 147·0 g. of the ester (Bischoff, *Annalen*, 1892, **214**, 38) to a cooled solution of 13·7 g. of sodium in excess of absolute alcohol. After the alcohol had been removed at the water-pump, the residue was dried at 100°/2 mm. for two days. The powdered sodium derivative (154 g.) was boiled under reflux with 182 g. of *cyclo*hexyl bromide in 230 c.c. of dry xylene for 19 hours. The solution was cooled, washed well with water, and dried (Na_2SO_4), and the xylene and excess of *cyclo*hexyl bromide were removed at the water-pump. Fractionation of the residue yielded 112 g. of material, b. p. 143—158°/1—2 mm., and after redistillation, 91 g. of b. p. 195—198°/13—14 mm. (50%).

*cyclo*Hexylsuccinic Acid (I).—This acid was prepared by refluxing a mixture of 31·7 g. of the above ester, 300 c.c. of concentrated hydrochloric acid, and 10 c.c. of alcohol for 48 hours. The acid crystallised directly from the cold solution; yield 19·1 g. (99%), m. p. 144—146°. It crystallised from ether–light petroleum in small colourless prisms, m. p. 144—145° (Swain, Todd, and Waring, *loc. cit.*, give m. p. 146—147° for acid made by a different method). The preliminary condensation is much more efficient when carried out in this way than in boiling alcohol, for which Ranganathan (*loc. cit.*) quotes a yield of 25% of an ester, giving a 67% yield of the acid (I).

The anhydride was distilled from a mixture of 10·0 g. of the acid and 25 c.c. of acetic anhydride which had been heated for two hours on the steam-bath. It boiled at 164—165°/8 mm. and solidified to a white crystalline solid, m. p. 34·5—35·5°; yield, 8·9 g. (97%). From ether–light petroleum it formed large colourless tablets, m. p. 35—36° (Ranganathan gives m. p. 42°). The *acid-p-toluidide* (probably IV; R = H), formed by addition of an equivalent quantity of *p*-toluidine to the anhydride in benzene, was purified by solution in aqueous sodium hydrogen carbonate, precipitation with acid, and crystallisation from dilute alcohol. It formed colourless needles melting with decomposition at 187—188°, when the capillary was heated very slowly (Ranganathan, m. p. 187°). By treatment of the acid-*p*-toluidide with diazomethane in ether the *methyl ester p-toluidide* (probably IV; R = CH_3) was formed quantitatively. From dilute alcohol it yielded colourless needles, m. p. 120—121° (Found: C, 71·4; H, 8·1. $C_{15}H_{20}O_3N$ requires C, 71·25; H, 8·3%).

*cyclo*Hexylsuccinic *Half Methyl Ester* (II and III; R = OH).—A standard solution of sodium methoxide in methanol (0·816N.; standardised against potassium acid phthalate) (135 c.c.) was added to a chilled suspension of *cyclo*hexylsuccinic anhydride (19·95 g.) in methanol. The alcohol was then removed at 40° (water-pump), and the crystalline residue of sodium salt was dissolved in water, and the solution filtered, washed once with ether, and treated with a slight excess of hydrochloric acid. The precipitated oily half-ester was taken up in ether, washed with water, and dried first over sodium sulphate and finally, after removal of the solvent, in a vacuum desiccator (Found: on two different samples, equiv., 219, 212·2. Calc.: 214·2).

When submitted to vacuum distillation the half-ester partially decomposed into methanol and the anhydride, indicated by a depression of the equivalent. Also, when distilled material was converted into the acid chloride, some dichloride, evidently arising from anhydride, appeared to be present, since a *di-p-toluidide* was isolated on treatment with *p*-toluidine. From methanol it formed long felted needles, m. p. 250—250·5° (without decomp.) (Found: N, 7·7. $C_{21}H_{26}O_3N_2$ requires N, 7·4%).

The half benzyl ester was prepared by treating the anhydride with sodium benzyloxide prepared according to Bischoff (*Ber.*, 1903, **36**, 159) by heating equivalent quantities of sodium and benzyl alcohol in benzene. The formation of sodium benzyloxide was incomplete and consequently the yield of half-ester was diminished. On long storage the oily ester deposited some crystals which were triturated with light petroleum and recrystallised from ether–light petroleum; bold colourless prisms, m. p. 60—61°.

*cyclo*Hexylsuccinic *half methyl ester acid chloride* (II and III; R = Cl) was prepared by treating the above half methyl ester with an excess of thionyl chloride, purified according to Fieser ("Experiments in Organic Chemistry," D. C. Heath and Co., 1935). Next morning the mixture was warmed to 40—50° for one hour and fractionated. The acid chloride distilled at 117—118°/2—3 mm. as a colourless liquid; yield, 23·4 g. (91·5% from anhydride) (Found: Cl, 15·3. $C_{11}H_{17}O_3Cl$ requires Cl, 15·2%).

A mixture of ester *p*-toluidides was formed by treatment of the acid chloride in acetone with an excess of *p*-toluidine. On addition of dilute hydrochloric acid the crude *p*-toluidides separated as an oil and solidified when scratched. After crystallisation the material formed colourless felted needles from dilute alcohol, melting indefinitely between 130° and 140°. A sample was treated with alcoholic aqueous alkali for two hours at room temperature. After dilution with water a solid residue was filtered off. It crystallised from dilute alcohol in glistening colourless needles. This material, m. p. 164·5—165°, was identical with a sample of the *p*-tolylimide prepared by vacuum distillation of the acid *p*-toluidide obtained by addition of *p*-toluidine to the anhydride as described above.

The crude mixture of acid *p*-toluidides was precipitated from the aqueous solution (after the removal of the tolylimide) by the addition of mineral acid. After dissolution in and reprecipitation from bicarbonate solution, the recrystallised material formed colourless needles from dilute alcohol, and had m. p. 187—188° (decomp.) when heated very slowly. No depression was observed on mixing with a sample of the homogeneous acid *p*-toluidide (VII; R = H) obtained above. However, the new material cannot be homogeneous because methylation with diazomethane regenerated a mixture of ester *p*-toluidides, m. p. *ca.* 125—140°, similar to that described above.

Methyl β-Formyl-α-cyclohexylpropionate.—The mixture of acid chlorides (II and III; R = Cl) (8·7 g.) in 40 c.c. of dry xylene was reduced according to the same procedure as used for the succinic acid derivative in the presence of 1 g. of catalyst and 3 mg. of poison.* The bath-temperature did not exceed 114°. In 1½ hours 50% of the hydrogen chloride was liberated, and in the next 1½ hours a further 27%. The reaction had then almost ceased. The mixture was cooled, treated with Norite, filtered, and fractionated. The aldehyde distilled at 124—130°/4—5 mm. as a colourless liquid; yield 5·4 g. (73%). This was immediately added to a methanol solution of semicarbazide, prepared by warming a suspension of equal weights of semicarbazide hydrochloride and sodium hydrogen carbonate in methanol at 40° until all the carbon dioxide was evolved, and filtering off the sodium chloride. On the addition of water the mixture of semicarbazones crystallised; yield, 6·1 g. (88·5%), m. p. *ca.* 104—128°. When the mixture was crystallised slowly from dilute methanol the less soluble isomeride separated in colourless microscopic rods, m. p. 150—151°; yield, 2·8 g. After one recrystallisation the *semicarbazone* of *methyl β-formyl-α-cyclohexylpropionate* (V) melted constantly at 150·5—151° (Found: C, 56·6; H, 8·1. $C_{12}H_{21}O_3N_3$ requires C, 56·45; H, 8·3%).

The concentrated mother-liquor yielded on standing overnight the isomeric semicarbazone, 2·5 g., m. p. 110—115°. One recrystallisation from dilute alcohol gave 1·9 g. of needles, m. p. 114—117°. A sample recrystallised several times yielded the pure semicarbazone of methyl β-formyl-β-*cyclo*hexylpropionate (VI), m. p. 118—119°. A mixed melting point with a sample of Elderfield's semicarbazone (m. p. 118—119°) showed no depression.

Formylation of cycloHexylsuccinic Ester.—Dimethyl *cyclo*hexylsuccinate was prepared by refluxing 39 g. of the acid (I) with 150 c.c. of methanol and 6 c.c. of sulphuric acid for 6 hours. Isolated as usual, the ester boiled at 122—125°/2 mm.; yield, 40 g., 89%.

Anhydrous alcohol (13 c.c.) was added to 200 c.c. of dry ether containing 5 g. of sodium wire. At the end of the reaction (overnight) a mixture of 40 g. of the above ester and 17 g. of freshly distilled ethyl formate was added. After 2 days at room temperature, the product was decomposed with 50 g. of ice and 60 c.c. of 20% sulphuric acid. The aqueous layer was removed and extracted with ether. The united ethereal solution was then extracted with three successive portions of 50 c.c. of cold saturated aqueous potassium carbonate. The aldehydic ester was recovered from the alkaline extract by acidification, ether extraction, and distillation. The product (VII) was a viscous oil boiling over a considerable range (compare Carrière, *loc. cit.*) but mainly in the range 145—155°/2—3 mm. All fractions gave a red colour with alcoholic ferric chloride. This was most intense with the lower-boiling fractions, which presumably contained most of the enol. When the ethereal layer which had been extracted with carbonate was allowed to stand for two days and was again extracted with potassium carbonate, a further quantity of the formyl ester was recovered, indicating the formation of more enolic material on standing. Total yield: 14·4 g. (32%).

β-Formyl-α-cyclohexylpropionic Acid (VIII).—The formyl ester (VII) (2 g.) was heated with 1·5 g. of oxalic acid and 5 c.c. of water for 5 hours in a slow current of steam, by which time the evolution of carbon dioxide had ceased. The residue was extracted with ether, and the extract washed with calcium acetate solution and water, and dried (Na_2SO_4). The residue from the ether distilled between 130° and 155°/2—3 mm. as a viscous oil which was converted into a *semicarbazone* in the usual way. This separated at 0° as a flocculent precipitate which after crystallisation from dilute alcohol had m. p. 175—175·4°; yield 0·3 g. (16%). It was soluble in aqueous sodium carbonate but insoluble in water (Found: C, 55·3; H, 7·9. $C_{11}H_{19}O_3N_3$ requires C, 54·8; H, 7·9%).

The semicarbazone was esterified with diazomethane in methanol. It yielded the methyl ester semicarbazone (V) which melted at 149—150° alone or mixed with the corresponding substance prepared through the Rosenmund method.

Samples of the ester-semicarbazone prepared by both procedures were warmed with an alcoholic solution of 2:4-dinitrophenylhydrazine. The yellow crystals so formed were then recrystallised from alcohol. Both products melted at 132—133° after a partial melting at 111—112°. After a further crystallisation from acetic acid the pure 2:4-*dinitrophenylhydrazone* of *methyl β-formyl-α-cyclohexylpropionate* was obtained from both samples, melting sharply at 132·5—133° (Found: C, 54·2; H, 5·8. $C_{17}H_{23}O_6N_4$ requires C, 54·0; H, 5·9%).

Hydrolysis of the formyl ester (VII) with hydrogen bromide in acetic acid yielded *cyclo*hexylsuccinic acid (m. p. 143—144°) and an unsaturated lactone not yet fully investigated. This lactonisation has since been studied by Swain, Todd, and Waring (*loc. cit.*).

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* It seems necessary to determine the optimum amounts of catalyst and poison before the reduction is started. The introduction of additional catalyst after the reaction is in progress has no apparent effect on the rate of reduction. Thus, when the components were mixed with too much poison to permit any reduction to begin, additional catalyst did not serve to initiate the reaction.

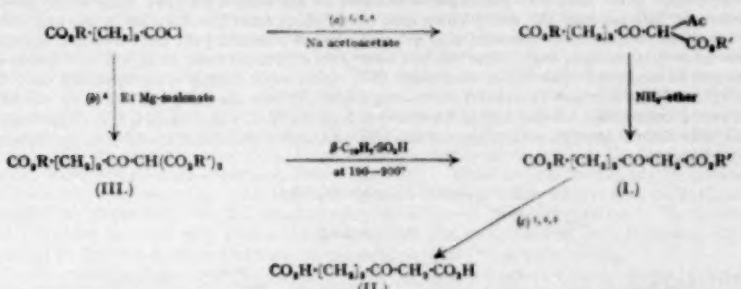
460. *Unsaturated Lactones and Related Substances. Part III. α-Ketoadipic Acid and γ-Carboxymethylenebutanolide.*

By Ulli Eisner, J. A. Elvidge, and R. P. Linstead.

A two-stage process for the preparation of β-ketoadipic acid (II) in 70—80% overall yield from (readily available) β-carbethoxypropionyl chloride is described. Cyclodehydration of (II) to γ-carboxymethylenebutanolide (V) is best effected with acetyl chloride–hydrogen chloride: under other conditions the corresponding lactonic acid anhydride (IV) is obtained, which with water affords (V) and (II), and with methanol, methyl β-ketoadipate and (V). Hot acetic anhydride reacts with (V) to yield the mixed anhydride with acetic acid (VII). The structure of the lactonic acid (V) is proved by its oxidation to oxalic and succinic acids. The lactone ring of (V) is opened by water, methanol containing hydrogen chloride, aqueous ammonia, and aniline to give respectively β-ketoadipic acid, methyl lævulate, lævulamide, and lævulanilide. The lactonic ester (VI) reacts with aniline to form methyl β-anilidopropionylacetate and with sodium methoxide in methanol to form methyl β-ketoadipate. Hydrogenation of the unsaturated lactonic acid (V) yields only adipic acid, and no saturated lactonic acid.

The dehydration of γ-keto-acids is a standard method of making unsaturated γ-lactones (see, *e.g.*, Kuehl, Linstead, and Orkin, Part I, *J.*, 1950, **2213**). We have now examined the possibility of obtaining an unsaturated lactonic acid from a keto-dibasic acid. The product is of interest as having a double bond in an unusual position, exocyclic to the γ-lactone ring; moreover, the presence of a free carboxyl provides a functional group capable of modification and thus increases the possible range of variation in physiological activity.

The acid selected for study was β-ketoadipic acid. Its esters (I) have been prepared from the half-esters, half-chloride of succinic acid by the routes (*a*) and (*b*), and the acid itself (II) by their hydrolysis (*c*) with cold concentrated hydrochloric acid:



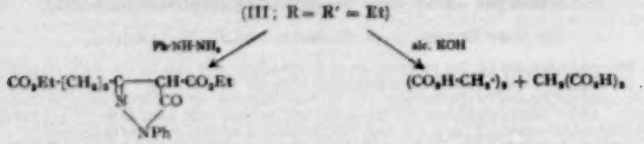
[1] Bardhan, *J.*, 1936, 1848.
[2] Ruggli and Maeder, *Helv. Chim. Acta*, 1942, **25**, 936.
[3] Stevens and Beutel, *J. Amer. Chem. Soc.*, 1943, **65**, 449.
[4] Riegel and Lilienfeld, *ibid.*, 1945, **67**, 1273.
[5] Richter, *Helv. Chim. Acta*, 1949, **32**, 2318.

Yields of (I):
unstated (R = R′ = Me)
27% (R = Me, R′ = Et)
11% (R = R′ = Et)
40% ,,

The decarbethoxylation stage of method (*b*) gave very variable results in our hands and the overall yield of ethyl β-ketoadipate (I; R = R′ = Et) was seldom more than 16%. We therefore examined Lukeš, Kastner, Gut, and Herben's synthesis (*Coll. Czech. Chem. Comm.*, 1947, **12**, 647). These authors found that ethanolysis of the readily available benzoyl derivative of furfuraldehyde cyanohydrin gave 45% of a product which contained ethyl β-ketoadipate, although this could not readily be isolated in a state of purity. We have confirmed this result and the method offers no advantage.

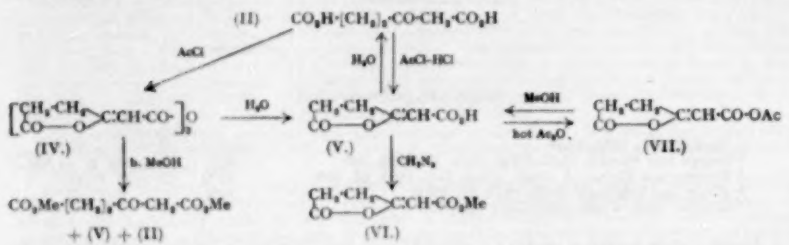
We next attempted to modify Riegel and Lilienfeld's synthesis (*b*) by isolating the intermediate triester (III) and hydrolysing this directly to β-ketoadipic acid. This route proved highly satisfactory. From the reaction of β-carbethoxypropionyl chloride with ethyl magnesiomalonate, ethyl β-keto-α-carbethoxyadipate (III; R = R′ = Et) was easily separated by vacuum distillation, in yields of 70—80%. The triester was characterised by formation of

the phenylpyrazolone, and the structure was proved by hydrolysis with cold alcoholic potassium hydroxide to malonic and succinic acids, which were isolated quantitatively :



Treatment of the triester (III; R = R′ = Et) with cold concentrated hydrochloric acid, followed by evaporation of the solution to dryness at 30—35° under reduced pressure, readily afforded β-ketoadipic acid (II) in quantitative yield. Previous workers, when effecting the similar stage (*c*) (above), have isolated the β-ketoadipic acid by evaporation of the hydrolysate over potassium hydroxide in a vacuum desiccator at room temperature, a process which even on the quite small scale is unduly lengthy.

Lactonisation of β-Ketoadipic Acid.—First attempts to lactonise β-ketoadipic acid by heating it with acetyl chloride afforded mainly a neutral product, $C_{12}H_{16}O_7$, m. p. 164°, which gave no coloration with ferric chloride, unlike β-ketoadipic acid or its esters which give, respectively, a purple and a deep red. It appeared to be the anhydride (IV) of the required lactonic acid. In agreement with this formulation, the substance was found to react with water at room temperature, yielding the desired lactonic acid, $C_6H_6O_4$. This also failed to give an immediate coloration with ferric chloride, but after being warmed with water the solution gave a reddish colour with that reagent. This corresponds to the hydrolysis of the lactonic acid to β-ketoadipic acid, a reaction which was subsequently demonstrated by the isolation of the latter as the sole product. Treatment of the lactonic acid with ethereal diazomethane afforded the crystalline methyl ester (VI). Suitably prolonged treatment of the anhydride (IV) with water gave a mixture of lactonic acid (V) and β-ketoadipic acid, whilst from the reaction of the anhydride with boiling methanol, the lactonic acid (V) and methyl β-ketoadipate were isolated, together with some β-ketoadipic acid. The methyl ester (VI) of the lactonic acid was not obtained. The results suggested that the lactonic ester (VI) reacts more readily with methanol than the acid (V). In an attempt to convert the lactonic acid (V) into the anhydride (IV) by warming with acetic anhydride, a high yield of the mixed anhydride (VII) was obtained. With methanol, (VII) afforded the lactonic acid (V) quantitatively : the other product of reaction was presumbly methyl acetate.

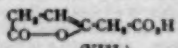


When β-ketoadipic acid was heated with redistilled acetyl chloride or treated for longer periods with acetic anhydride at room temperature, 70% yields of a crude solid were obtained. By fractional crystallisation, the lactonic acid (V) was isolated in about 10% yield : the remainder of the material consisted of a mixture of the anhydride (IV) with a small amount of another neutral substance of m. p. 189°, which was sparingly soluble in the common solvents. From its analysis and ultra-violet light absorption spectrum this substance appeared to be isomeric with the anhydride, but it was recovered unchanged after treatment with cold water. Lack of material precluded its further investigation.

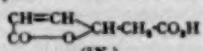
Treatment of β-ketoadipic acid with acetic acid which had been saturated with dry hydrogen chloride proved abortive, since the starting material was recovered. Treatment at room temperature with acetyl chloride containing hydrogen chloride, however, afforded the lactonic

acid as main product. By this method the pure lactonic acid (V) could readily and consistently be obtained from β-ketoadipic acid in 40—50% yield.

The structure of the lactonic acid was determined by oxidation with potassium permanganate. Succinic acid and oxalic acid were isolated in high yield, proving that the formulation as γ-carboxymethylenebutanolide (V) was correct. The isomeric lactonic acids (VIII) and (IX) would not give succinic acid under the conditions employed.



(VIII.)



(IX.)

During the course of this work a communication by Richter appeared (*Helv. Chim. Acta*, 1949, **32**, 2318) which described the preparation of the lactonic acid methyl and ethyl esters from the corresponding half esters of β-ketoadipic acid (I; R = H) by cyclisation under comparatively vigorous conditions. Richter's description of the lactonic methyl ester indicated that it was identical with our product (VI), and consequently his oxidation results, *e.g.*, formation of oxalic acid, and of succinic acid and its anhydride on ozonolysis, also serve to support the exocyclic double-bond structure (V) for the lactonic acid. Very recently, Richter (*ibid.*, 1950, **33**, 20) has claimed the preparation of the lactonic acid (V) in 2·5% yield by treating methyl ethyl β-ketoadipate (I; R = Me, R′ = Et) with concentrated sulphuric acid. We think it highly probable, however, from his description of the product, its melting point, and failure to react with diazomethane or immediately with aqueous sodium carbonate, that it is not the lactonic acid (in spite of the analysis quoted) but is identical with the anhydride (IV) described above.

The lactonic acid (V) has a γδ-double bond exocyclic to a γ-lactone ring. In most of its reactions, it resembles a βγ- rather than an αβ-unsaturated γ-lactone. For instance, when it was refluxed with dry methanol containing a trace of hydrogen chloride, methyl lævulate was formed, being isolated in 43% yield as its 2 : 4-dinitrophenylhydrazone. With boiling absolute methanol alone, (V) underwent no change during 2·5 hours, while even after being refluxed with methanol containing 0·5% of water, it was recovered very largely unchanged. The slow ring-opening with cold water to β-ketoadipic acid has already been mentioned. After treatment of (V) with concentrated aqueous ammonia, followed by vacuum evaporation at room temperature, a white deliquescent solid was obtained. With water, or on being warmed with organic solvents, this material evolved carbon dioxide and afforded a neutral product identified as lævulamide : with acid 2 : 4-dinitrophenylhydrazine solution it gave the dinitrophenylhydrazone of lævulic acid. On keeping the lactonic acid (V) with aniline in a solvent lævulanilide was formed, and the lactonic ester (VI) under these conditions gave methyl β-anilidopropionylacetate (compare βγ-angelicalactone, Part I, *loc. cit.*). With sodium methoxide in absolute methanol the lactonic ester (VI) afforded methyl β-ketoadipate which was isolated and identified by conversion into the semicarbazone and known phenylpyrazolone. The lactonic acid (V) failed to react with *p*-nitrotoluene-ω-thiol. The ready loss of carbon dioxide which occurred in the ring-opening reactions of the lactonic acid (V) is noteworthy.

Hydrogenation of the ester (VI) in the presence of platinum resulted in an uptake of 2 mols. of hydrogen, and an oil was obtained which on warming with aqueous hydrochloric acid afforded adipic acid. Complete hydrogenation of the lactonic acid (V) under similar conditions gave adipic acid direct. 50% Hydrogenation of (V) gave a mixture of adipic acid and unchanged lactone (V). The behaviour on reduction of the unsaturated system present in (V) and (VI) resembled many of the results of Jacobs and Scott (*J. Biol. Chem.*, 1930, **87**, 601; 1931, **93**, 139), who found that αβ-unsaturated lactones gave normal dihydro-products but that many βγ-unsaturated γ-lactones were fully hydrogenated to deoxy-acids. However, β-substitution was a factor which reduced the capacity of Δ^{β}-lactones for this abnormal reaction. Our new lactonic acid (V) has the double bond next to the point of lactonisation and resembles Jacobs and Scott's simple βγ-unsaturated γ-lactones in its complete conversion into deoxy-acid.

Experimental.

Ethyl β-Keto-α-carbethoxyadipate.—According to the directions of Riegel and Lilienfeld (*loc. cit.*), β-carbethoxypropionyl chloride (60 g., b. p. 98°/15 mm.), prepared in 91% yield from succinic anhydride (40 g.; recrystallised from acetic anhydride), was added in ether (50 c.c.) to an ethereal solution (200 c.c.) of ethyl magnesiomalonate [from ethyl malonate (50·5 g.) and magnesium turnings (7·9 g.)], and the mixture refluxed and stirred for 4 hours. The mixture was cooled, and with continued stirring a cold solution of sulphuric acid (9·5 c.c.) in water (190 c.c.) was slowly added. The ethereal layer was separated, and the aqueous layer extracted once with ether. The combined ethereal solution was washed with a little water, dried (Na_2SO_4), and distilled, finally under reduced pressure. After a small

lorerun, ethyl β-keto-α-carbethoxyadipate (76·5 g.; 73% calculated on β-carbethoxypropionyl chloride) was collected as a colourless oil, b. p. 144°/0·2 mm., n_D^{20} 1·4506 (Found: C, 54·5; H, 7·0. $C_{12}H_{20}O_7$ requires C, 54·2; H, 7·6%). The ester gives a red coloration with aqueous ethanolic ferric chloride.

The ester (1 g.) in methanol was allowed to react overnight with phenylhydrazine (0·5 c.c.) in 50% acetic acid (5 c.c.), and the solution poured on ice. *Ethyl 5-keto-4-carbethoxy-1-phenylpyrazoline-3-β-propionate* separated from aqueous methanol as cream-coloured needles, m. p. 61—62° (Found: N, 8·5. $C_{17}H_{20}O_5N_2$ requires N, 8·4%).

Alkaline Hydrolysis of Ethyl β-Keto-α-carbethoxyadipate.—The ester (3 g.) was treated overnight with a solution of potassium hydroxide (3 g.) in methanol (10 c.c.), and the solution then acidified with aqueous hydrochloric acid and evaporated to dryness under reduced pressure. Extraction of the residue with acetone afforded a mixture of acids which was treated with ether (45 c.c.). The residue (0·89 g.) had m. p. 184° undepressed by succinic acid, whilst evaporation of the ether gave malonic acid (1·12 g.), m. p. 105—115°, which on recrystallisation had m. p. 136—137° alone and in admixture with an authentic specimen.

β-Ketoadipic Acid.—Ethyl β-keto-α-carbethoxyadipate (76·5 g.) was kept at room temperature with concentrated hydrochloric acid (200 c.c.) for 36 hours. Carbon dioxide was evolved. Distillation of the solution to dryness at 30—35° under reduced pressure afforded a white solid which was freed from some occluded hydrochloric acid by keeping it overnight in a vacuum desiccator containing potassium hydroxide: the β-ketoadipic acid (42 g., yield quantitative) had m. p. 115° (decomp.) and needed no further purification.

Lactonisation Experiments.—(*a*) *The anhydride* (IV). β-Ketoadipic acid (0·8 g.) and acetyl chloride (5 c.c.) were heated under reflux until evolution of hydrogen chloride ceased. On removal of the excess reagent under reduced pressure and addition of dry ether, the residue solidified and had m. p. 150—155°. From ethyl acetate the *anhydride* of γ-carboxymethylenebutanolide (γ-carboxymethylenebutyrolactone) crystallised as prisms, m. p. 164° (Found: C, 54·15; H, 3·75. $C_7H_6O_4$ requires C, 54·1; H, 3·8%). Light absorption in dry dioxan: maximum at 2470 A., ε = 50,540.

(*b*) β-Ketoadipic acid (3 g.) and freshly distilled acetyl chloride (25 c.c.) were heated under reflux for 2 hours. The solution was filtered from a trace of insoluble matter and concentrated under reduced pressure. Trituration of the oily residue with ether gave a white solid which was insoluble in aqueous sodium hydrogen carbonate and which gave no coloration with ferric chloride. From ethyl acetate the isomeric *anhydride* (?) crystallised as beautiful needles, m. p. 189° (Found: C, 54·4, 54·1; H, 3·9, 3·9. $C_7H_6O_4$ requires C, 54·1; H, 3·8%). Light absorption in dioxan: maximum at 2470 A., ε = 51,870. The compound was recovered unchanged (m. p. and mixed m. p. 185—189°) after treatment with water for 16 hours, and appeared not to react with boiling methanol (see below).

(*c*) β-Ketoadipic acid (10·9 g.) was kept with acetic anhydride (35 c.c.) for 3 days at room temperature. The solution was distilled under reduced pressure (bath temp. > 50°), and the residue treated with ether. On crystallisation from ethyl acetate some of the above isomeric compound was isolated, together with crude anhydride (IV) (2·8 g.), m. p. 145—147°.

(*d*) Hydrogen chloride was passed for 15 minutes into a suspension of β-ketoadipic acid (2 g.) in acetic acid (20 c.c.). After 3 days the solution was filtered and evaporated under reduced pressure. The solid residue (1·3 g.) was identified as β-ketoadipic acid by m. p. and the purple coloration afforded with aqueous ferric chloride.

(*e*) *γ-Carboxymethylenebutanolide* (*γ-carboxymethylenebutyrolactone*) (V). β-Ketoadipic acid (10·3 g.) was added to acetyl chloride (80 c.c.) (unredistilled and containing hydrogen chloride) at room temperature. After 24 hours the excess of reagent was distilled under reduced pressure, and the residue (9 g.) crystallised from ethyl acetate–light petroleum (b. p. 60—80°). Colourless needles (4·4 g.; 48%), m. p. 176—179° (decomp.), were obtained which dissolved with effervescence in aqueous sodium hydrogen carbonate and gave no coloration with aqueous ethanolic ferric chloride. Recrystallisation from ethyl acetate, or chloroform, gave silky needles of pure *γ-carboxymethylenebutanolide* with m. p. 184° (decomp.) (Found: C, 51·0, 50·7; H, 4·3, 4·4. $C_5H_4O_4$ requires C, 50·7; H, 4·25%). Light absorption in dioxan: maximum at 2260 A., ε = 19,310.

A second preparation from β-ketoadipic acid (15 g.) and acetyl chloride (150 c.c.) gave a crude solid (8·25 g.) which on crystallisation from ethyl acetate–light petroleum (b. p. 60—80°) afforded needles, m. p. 176—177° (decomp.), of the lactonic acid (V) (6 g.) in 45% yield. Such material was sufficiently pure for further use.

γ-Carbomethoxymethylenebutanolide (VI).—Treatment of the lactonic acid (V) with ethereal diazomethane and evaporation of the solution under reduced pressure yielded a neutral solid. γ-Carbomethoxymethylenebutanolide formed laths, m. p. 110°, from ether–light petroleum (b. p. 40—60°) (Found: C, 53·9, 54·2; H, 4·7, 5·3. Calc. for $C_7H_8O_4$: C, 53·9; H, 5·1%). Richter (*Helv. Chim. Acta*, 1949, **32**, 2318) records m. p. 108°.

Oxidation of γ-Carboxymethylenebutanolide.—Potassium permanganate (0·90 g.; 3 atoms of O) in water (35 c.c.) was added during 1·5 hours to a stirred solution of the lactonic acid (0·40 g.) in 2·5% aqueous sodium hydrogen carbonate (30 c.c.) kept at 0° to −2°. Water (30 c.c.) was added, the mixture was warmed to coagulate manganese dioxide and filtered, and the residue extracted with warm 1% aqueous sodium hydrogen carbonate (20 c.c.). The combined filtrate was acidified with dilute hydrochloric acid, the reaction adjusted to pH 4 with ammonia, and concentrated calcium chloride solution (5 c.c.) added. The white precipitate of calcium oxalate was collected, washed with water, and dried to constant weight; yield, 0·279 g. (77%). Treatment with 2N-sulphuric acid (15 c.c.) and extraction with ether (7 times) afforded oxalic acid (0·159 g.), m. p. and mixed m. p. 100° with resolidification and m. p. 185—188° (decomp.). The filtrate from the calcium oxalate was extracted continuously with ether for

20 hours. Evaporation of the ether gave a completely crystalline residue (0·229 g.; 69%), which was soluble with effervescence in aqueous sodium hydrogen carbonate, and had m. p. 184—185° alone or in admixture with succinic acid.

Reactions of the Anhydride (IV).—(a) *With water.* The anhydride (185 mg.) was treated with a little water which was then removed *in vacuo* over sulphuric acid. Repetition of the treatment afforded a residue, m. p. 173—176° (decomp.), which on recrystallisation from ethyl acetate–light petroleum (b. p. 60—80°) had m. p. 185° (decomp.) undepressed in admixture with γ-carboxymethylenebutanolide. Further treatment of the residue with aqueous acetone, followed by evaporation, gave β-ketoadipic acid, m. p. 115—120° (decomp.) (purple ferric chloride colour).

(b) *With methanol.* The anhydride (2·8 g.; crude) and excess of methanol were heated under reflux for 4 hours. When the solution was cooled, the neutral isomeric compound (0·44 g.), m. p. 172—174°, separated. The filtrate was evaporated under reduced pressure, the residue dissolved in ethyl acetate, and the solution extracted with saturated aqueous sodium hydrogen carbonate (12 c.c.). Evaporation of the ethyl acetate left a neutral oil which failed to crystallise, gave a strong red coloration with aqueous ethanolic ferric chloride, and was evidently methyl β-ketoadipate. On cautious acidification of the aqueous extract, γ-carboxymethylenebutanolide (0·29 g.) separated, m. p. 180° (decomp.). Concentration of the mother-liquors in a vacuum desiccator yielded β-ketoadipic acid (0·7 g.), m. p. 117° (decomp.) (purple ferric chloride colour).

Reactions of γ-Carboxymethylenebutanolide and its Methyl Ester.—(a) *With acetic anhydride.* A solution of the lactonic acid (1 g.) in acetic anhydride (15 c.c.) was heated on the steam-bath for 3 hours. Evaporation under reduced pressure gave an oil which on trituration with a small volume of dry ether set solid (1 g.), m. p. 70—80°. From ether–light petroleum (b. p. 60—80°) the *mixed anhydride* (VII) of γ-carboxymethylenebutanolide with acetic acid separated as shiny plates, m. p. 72° (Found: C, 52·2; H, 4·3. $C_9H_8O_5$ requires C, 52·2; H, 4·35%). The compound dissolved gradually in aqueous sodium hydrogen carbonate and gave no coloration with aqueous ethanolic ferric chloride.

A solution of the mixed anhydride (0·5 g.) in methanol (5 c.c.) was kept at room temperature overnight and then evaporated under reduced pressure. The completely crystalline residue gave no coloration with ferric chloride and had m. p. 172—175° (decomp.) undepressed by γ-carboxymethylenebutanolide.

The lactonic acid (0·3 g.) was kept overnight with acetic anhydride (3 c.c.). On removal of the solvent under reduced pressure a solid was obtained (0·3 g.), m. p. 154—158°, which after crystallisation (twice) from ethyl acetate had m. p. 189° alone and in admixture with the "isomeric anhydride" described above.

(b) *With water.* The lactonic acid (0·4 g.), dioxan (3·5 c.c.), and water (2·5 c.c.) were kept at room temperature for 3 days. Undissolved lactonic acid (0·115 g.), m. p. 170—174° (decomp.) (no ferric chloride colour), was collected, and the filtrate evaporated *in vacuo* over calcium chloride to yield readily water-soluble β-ketoadipic acid (0·30 g.), m. p. 109—111° (decomp.) (purple colour with ferric chloride).

(c) *With methanol.* (i) The lactonic acid (0·544 g.) was recovered unchanged (m. p. 182—183°, decomp.) after being refluxed with methanol (20 c.c.; dried over magnesium methoxide) for 2·5 hours. (ii) The recovered lactonic acid was heated under reflux for 2·5 hours with methanol (20 c.c.) containing 0·5% of water. Removal of the solvent under reduced pressure left a crude solid, m. p. 157—160° (decomp.), which gave a faint red coloration with aqueous ethanolic ferric chloride. Recrystallisation from chloroform yielded the lactonic acid, m. p. 185° (decomp.). (iii) A solution of the lactonic acid (0·7 g.) in dry methanol (20 c.c.) containing a trace of dry hydrogen chloride was refluxed for 2·5 hours, and then evaporated under reduced pressure. The residue was a neutral oil (red ferric chloride colour): it reacted with an alcoholic solution of 2 : 4-dinitrophenylhydrazine sulphate to yield the dinitrophenylhydrazone of methyl lævulate (0·67 g.; 43%), m. p. 130—131° raised to 138° on recrystallisation from methanol. A mixture with an authentic specimen had m. p. 138°. (iv) The lactonic acid methyl ester (VI) (1·53 g.) was added to a solution of sodium (0·23 g.; 1 mol.) in dry methanol (50 c.c.), and after 10 minutes the solvent was removed under reduced pressure and the residue treated with dilute hydrochloric acid and ether. The ether was washed with aqueous sodium hydrogen carbonate and evaporated to give an oil (1·18 g.; 64%). This reacted with alcoholic semicarbazide hydrochloride in the presence of aqueous sodium acetate to yield the *semicarbazone* of methyl β-ketoadipate (plates, m. p. 109°, from benzene, identical with a preparation from authentic methyl β-ketoadipate) (Found: N, 17·25. $C_9H_{15}O_5N_3$ requires N, 17·1%) and the known methyl 1-carbamido-5-ketopyrazoline-3-β-propionate which formed prismatic needles, m. p. 171°, from ethanol. Ruggli and Maeder (*Helv. Chim. Acta*, 1942, **25**, 961) gave m. p. 172°.

(d) *With ammonia.* A solution of the lactonic acid (0·6 g.) in concentrated ammonia (10 c.c.; *d* 0·88) was kept for 4 days and then evaporated to dryness over sulphuric acid, whereupon a deliquescent white solid was obtained. This material evolved carbon dioxide on treatment with organic solvents or water. Evaporation of the aqueous solution afforded somewhat impure lævulamide, m. p. 95—96° (decomp.), which with aqueous 2 : 4-dinitrophenylhydrazine hydrochloride gave a mixture of acidic and neutral derivatives. From methanol, the dinitrophenylhydrazone of lævulic acid formed red needles, m. p. 198° (Found: C, 45·1; H, 4·4; N, 19·4. Calc. for $C_{11}H_{12}O_6N_4$: C, 44·6; H, 4·1; N, 18·9%). A mixture with an authentic specimen (m. p. 206°) had m. p. 201°. The neutral derivative (probably of lævulamide), m. p. *ca.* 198°, could not be adequately purified.

(e) *With aniline.* (i) A solution of the lactonic acid (0·71 g.) and aniline (0·9 c.c.; 2 mols.) in dry dioxan was kept at room temperature overnight, then evaporated under reduced pressure. The residual oil slowly solidified: after being washed with ether, the solid (0·75 g.) was crystallised from benzene to give lævulanilide, m. p. 101—102° (Found: N, 7·55. Calc. for $C_{11}H_{13}O_2N$: N, 7·3%). (ii) A solution of the lactonic acid methyl ester (VI) (135 mg.) and aniline (100 mg.) in alcohol (3 c.c.) was kept at room

temperature for 2 days and then evaporated *in vacuo*. Recrystallisation of the solid from benzene–hexane afforded *methyl β-anilidopropionylacetate* (30 mg.), m. p. 86·5—87·5° (Found: C, 62·85; H, 6·1; N, 5·7. $C_{13}H_{15}O_4N$ requires C, 62·65; H, 6·0; N, 5·6%).

Hydrogenation of γ-Carboxymethylenebutanolide and its Methyl Ester.—(*a*) The lactonic ester (0·182 g.) in alcohol was hydrogenated at ordinary temperature and pressure in the presence of Adams's catalyst (uptake of hydrogen: 53·1 c.c. at 25°/767 mm. Calc. for uptake of 2 mols.: 51·2 c.c.). After filtration and evaporation of the alcohol, the oily residue was taken up in 10% hydrochloric acid, and the solution evaporated to dryness on the steam-bath. The crystalline residue (90 mg.) had m. p. 147—150° undepressed by adipic acid.

(*b*) Hydrogenation of the lactonic acid (0·71 g.) in dry dioxan (35 c.c.) at ordinary temperature and pressure in the presence of Adams's catalyst (150 mg.) occurred slowly and was complete in 8 hours. After filtration from catalyst, the solvent was removed under reduced pressure and the solid residue (0·65 g.), crystallised from water, had m. p. 150—151° alone and in admixture with adipic acid.

(*c*) The lactonic acid (0·7 g.) in dry dioxan (50 c.c.) was 50% hydrogenated at ordinary temperature and pressure in the presence of Adams's catalyst (100 mg.). The allowed uptake of hydrogen (120 c.c. at 15°/759 mm.) took 3 hours. The solution was then filtered, evaporated to dryness under reduced pressure, and the residue fractionally crystallised from ethyl acetate by addition of small volumes of light petroleum (b. p. 60—80°) to yield: (i) Prisms (0·29 g.; 51%), m. p. 147—150° undepressed by adipic acid; (ii) a mixture (51 mg.), m. p. 130—155°, and (iii) unchanged lactonic acid (0·33 g.; 94%), m. p. and mixed m. p. 173—178° (decomp.).

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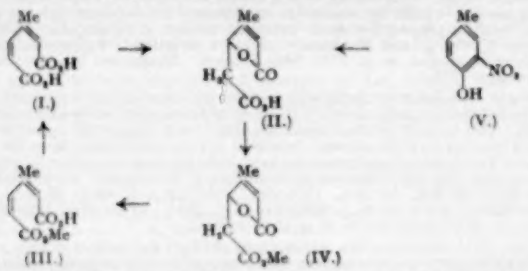
461. *Unsaturated Lactones and Related Substances. Part IV. Lactonic Products derived from Muconic Acid.*

By J. A. ELVIDGE, R. P. LINSTEAD, B. A. ORKIN, PETER SIMS, and (in part) HAROLD BAER and DEXTER B. PATTISON.

Lactonisation of *cis-cis*-muconic acid with sulphuric acid (*trans-trans*-muconic acid fails to react) gives mainly γ-carboxymethyl-Δ^{α}-butenolide (VI), the structure of which has been proved by hydrolysis to lævulic acid, and oxidation to oxalic and malic acids. Unlike the isomeric γ-carboxymethylidenebutanolide (Part III) by which (VI) is accompanied, the new lactonic acid (VI) is stable to water, acids, and weak bases. Hydrogenation of (VI) proceeds normally to γ-carboxymethylbutanolide (XI), the methyl ester (XII) of which is converted by hot sodium hydrogen carbonate solution into *trans*-Δ^{α}-dihydromuconic acid (XIII). The same acid (XIII) is obtained by hydrolysis of a methyl hydrogen Δ^{α}-dihydromuconate which is formed by isomerisation of (XII) with sodium methoxide in methanol. An isomeric methyl hydrogen Δ^{α}-dihydromuconate has been synthesised from β-carbomethoxypropaldehyde by the Doebner reaction. Various aspects of the literature on derivatives of muconic acids have been revised in the light of the new results.

As a by-product of the original lactonisation there is obtained the saturated dicyclic dilactone (XVI).

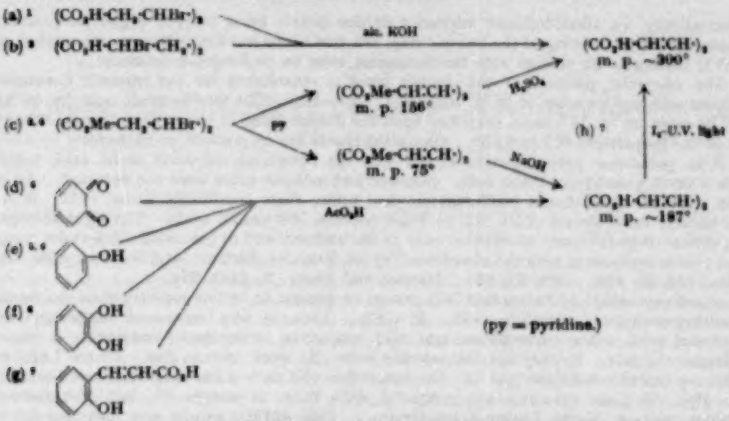
ONE of the standard methods of forming γ-lactones is to effect the isomerisation of Δ^{β}- or Δ^{γ}-unsaturated acids by distillation or by treatment with acids. Pauly and Will (*Annalen*, **1918**, **416**, 1) showed that this route could be applied to the lactonisation of β-methylmuconic acid (I) which under a variety of conditions readily gave the unsaturated lactonic acid (II).



The methylmuconic acid (I) was obtained by hydrolysis of the half methyl ester (III), which in turn had resulted from an interesting reaction, the treatment of the lactonic ester (IV) with

sodium methoxide. The lactonic acid (II) and ester (IV) had previously been obtained (Pauly, Gilmour, and Will, *ibid.*, 1914, **403**, 119) by ring fission of 3-nitro-*p*-cresol (V) with sulphuric acid. Pauly and Will (*loc. cit.*) did not concern themselves with the stereochemistry of their methylmuconic acid (I), but it appeared to us that this was probably of primary importance, having a direct bearing upon the ease of isomerisation of (I) to the cyclic form (II). Further investigation of this system is in hand. The present communication is concerned with the simpler case of lactonisation of the unsubstituted muconic acids.

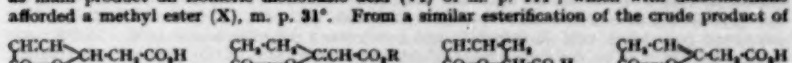
Two forms of muconic acid $(CO_2H{\cdot}CH{:}CH{\cdot})_2$ have been described, with melting points of approximately 300° and 187°. Methods of synthesising them are shown below:



[1] Rupe, *Annalen*, 1890, **256**, 1. [2] Ingold, *J.*, 1921, **119**, 981. [3] Farmer, *ibid.*, 1923, **123**, 2531. [4] Böeseken and Sloof, *Proc. Acad. Sci. Amsterdam*, 1929, **32**, 1043. [5] Böeseken and Engelberts, *ibid.*, 1931, **34**, 1292; Böeseken, *ibid.*, 1932, **35**, 750. [6] Böeseken and Kerkhoven, *Rec. Trav. chim.*, 1932, **51**, 964. [7] Grundmann, *Ber.*, 1936, **69**, 1755.

The configuration of the higher-melting form of muconic acid was shown to be *trans-trans* by Behrend (*Ber.*, 1916, **49**, 999) and Behrend and Heyer (*Annalen*, 1919, **418**, 294). They found that on permanganate oxidation *rac.*-tartaric acid was formed—*meso*-tartaric acid was specifically sought but could not be detected—and that on oxidation with sodium chlorate and osmium tetroxide mucic acid was produced, together with a small quantity of *rac.*-idosaccharic acid. The configuration of the lower-melting form of muconic acid as *cis-cis* was considered by Böeseken and Kerkhoven (*loc. cit.*) to have been demonstrated conclusively by its formation from *o*-benzoquinone [route (d)]. In addition, Böeseken and Kerkhoven showed that the tartaric acid formed on permanganate oxidation of this muconic acid was solely the *meso*-form.

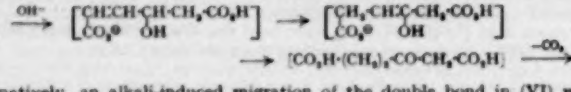
Our attempts to lactonise *trans-trans*-muconic acid [prepared by route (b) and characterised as the methyl ester] were unsuccessful. Under mild conditions sulphuric acid or a mixture of acetic acid and hydrogen chloride did not affect the acid, and under more vigorous conditions it appeared to be largely destroyed. On the other hand, *cis-cis*-muconic acid [prepared by route (e), and characterised by formation of the methyl ester, catalytic hydrogenation to adipic acid, and inversion to *trans-trans*-muconic acid] lactonised readily with sulphuric acid to yield as main product an isomeric monobasic acid (VI) of m. p. 111°, which with diazomethane afforded a methyl ester (X), m. p. 31°. From a similar esterification of the crude product of



lactonisation, besides (X), an isomeric methyl ester, m. p. 109°, was isolated in small quantity. The latter ester was identified with γ-carbomethoxymethylenebutanolide (VII; R = Me) obtained by lactonising β-ketoadipic acid (Eisner, Elvidge, and Linstead, *J.*, 1950, 2223). It

is possible that the lactonic acid (VI) has been obtained before though not in a pure state (see Beilstein, 4th Edn., **18**, 396).

That the new lactonic acid had a five-membered ring (VI), and not a six-membered ring such as (VIII), was shown by its hydrolysis with hot aqueous sodium hydroxide to lævulic acid, isolated as the semicarbazone. The hydrolysis very probably proceeds as follows :



Alternatively, an alkali-induced migration of the double bond in (VI) might have occurred before hydrolytic opening of the lactone ring, but this seems less likely because the methyl ester of (VI) undergoes no change with triethylamine, even on prolonged treatment.

The exocyclic position of the double bond is established for the isomeric unsaturated lactonic acid and its ester of m. p. 109° (VII; R = Me). The new lactonic acid (m. p. 111°) and its ester (m. p. 31°) must therefore have the double bond in the lactone ring in either the $\alpha\beta$- or the $\beta\gamma$-position (VI and IX). Oxidation shows the $\alpha\beta$-position to be correct.

With potassium permanganate in the cold the butenolide afforded oxalic acid, together with a small quantity of malic acid. Succinic and malonic acids were not detected. An acid with structure (IX) should yield malonic acid under these conditions, whilst (VII; R = H) has already been shown (Part III) to yield succinic and oxalic acids. The light-absorption properties—high-intensity absorption only at the extreme end of the usual ultra-violet range—were also in agreement with the structure (VI) (cf. Ruzicka, Plattner, and Heusser, *Helv. Chim. Acta*, 1942, **25**, 435; 1944, **27**, 186; Haynes and Jones, *J.*, 1946, 954).

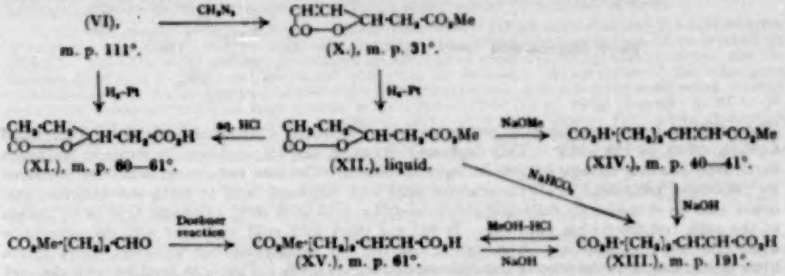
γ-Carboxymethyl-Δ^{α}-butenolide (VI) proved in general to be less reactive than the isomeric γ-carboxymethylenebutanolide (VII; R = H). Thus it was recovered unchanged after treatment with water, aqueous mineral acid, ammonia, or methanol containing a trace of hydrogen chloride. Neither did the lactonic ester (X) react with aniline. In the Légal test, under controlled conditions (pH 11), the butenolide (X) gave a less intense colour than (VII; R = Me). If these reactions are compared with those of simple Δ^{α}- and Δ^{β}-unsaturated lactones (see, *e.g.*, Kuehl, Linstead, and Orkin, *J.*, 1950, 2213) it will be seen that they fall into line with the Δ^{α}-structure for (VI).

On catalytic hydrogenation the butenolide (VI) absorbed only 1 mol. of hydrogen and gave an acid of m. p. 60—61°, analysis of which agreed with that for the saturated lactone (XI). Again, this result agrees with the Δ^{α}-structure (VI) since Jacobs and Scott (*J. Biol. Chem.*, 1930, **87**, 601) have shown that Δ^{α}-unsaturated γ-lactones are reduced to the corresponding saturated lactones whilst lactones derived from enolised keto-acids are abnormally hydrogenated to deoxy-acids.

Although the hydrogenation results were, thus, quite normal, yet they gave rise to certain subsidiary problems. The hydrogenation product, m. p. 60—61°, did not correspond with the compound which Leuchs and Möbis (*Ber.*, 1909, **42**, 1228) claimed to be the γ-lactone (XI) of β'-hydroxyadipic acid and which melted at 197—198° (201—202°, corr.). Moreover, a preparation due to Farmer (*J.*, 1923, **123**, 3324) was described as a colourless syrup. Furthermore, Farmer suggested that the acid which had been obtained by Leuchs and Möbis " was actually the isomeric Δ^{β}-dihydromuconic acid " (*trans*-Δ^{β}-dihydromuconic acid has m. p. 197°). Direct titration of our hydrogenation product (m. p. 60—61°) with alkali confirmed that it was indeed a monobasic acid. When, however, it was allowed to stand with an excess of alkali a further equivalent was consumed, evidently owing to the opening of the lactone ring. Hydrogenation of the methyl ester (X) of the original unsaturated lactonic acid gave the corresponding saturated lactonic ester (XII), a liquid which was hydrolysed with hot aqueous hydrochloric acid to the crystalline acid of m. p. 60—61°. Hydrolysis of the liquid ester (XII) with aqueous sodium hydrogen carbonate, on the other hand, gave an abnormal reaction : the lactone ring was opened and an isomeric mono-unsaturated dibasic acid of m. p. 191° was formed. This compound gave adipic acid on reduction and hence was a dihydromuconic acid. Direct comparison showed it to be the known *trans*-Δ^{α}-dihydromuconic acid (XIII) (Farmer and Hughes, *J.*, 1934, 1929, 1938; cf. Carrière, *Ann. Chim.*, 1922, **17**, 38). These results, which are summarised in the annexed scheme, prove that the hydrogenation product of (VI), m. p. 60—61°, is the γ-lactone (XI) of β'-hydroxyadipic acid.

With sodium methoxide in methanol, the saturated lactonic ester (XII) was readily isomerised to a monobasic unsaturated acid of m. p. 40—41°. The new product gave *trans*-Δ^{α}-dihydro-

muconic acid (XIII) on hydrolysis, and succinic acid on oxidation, and was therefore the hitherto undescribed methyl hydrogen *trans*-Δ^{α}-dihydromuconate (XIV). A methyl hydrogen *trans*-Δ^{α}-dihydromuconate with m. p. 60° had previously been obtained by Farmer and Hughes (*J.*, **1934**, 304, **1929**, **1938**) by partial esterification of the acid (XIII). Farmer and Hughes assigned the structure (XV) to their half-ester by analogy with the investigations of partial esterification by Sudborough and his collaborators (*J.*, **1911**, **99**, 2307 etc.), and Eccott and Linstead (*J.*, **1929**, 2153), who showed that carboxyl groups next to a double bond resisted

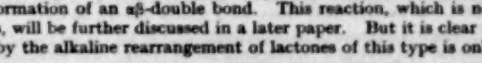


esterification. To clarify the structural position we have subjected β-carbomethoxypropaldehyde to the Doebner condensation with malonic acid. This yields a half ester of *trans*-Δ^{α}-dihydromuconic acid, m. p. 61°, undoubtedly identical with Farmer's product. Its structure is fully proved by the method of preparation and by the following facts: (*a*) on hydrogenation and hydrolysis it gives adipic acid; (*b*) on permanganate oxidation it yields methyl hydrogen succinate. Carrière (*loc. cit.*, p. 111) carried out a similar synthesis of Δ^{α}-dihydromuconic acid from succinaldehydic acid. Incidentally, he reports m. p. 208—210° for the product, which is higher than any recorded by other workers. Melting points in this series of compounds vary substantially with the rate of heating: our preparations of this Δ^{α}-acid melted at 190—191° with slow heating, and, in agreement with Farmer and Hughes (*loc. cit.*), never as high as Carrière's figure.

The rearrangement with alkali of the saturated lactonic ester (XII) to unsaturated open-chain material (XIII, XIV) presents an interesting difference from the normal tendency of lactones to yield open-chain hydroxy-compounds under similar conditions. When, however, the special structural peculiarities of these materials are considered, the reaction is seen to be not unexpected. Indeed, we have observed a similar isomerisation of the *unsaturated* lactonic ester (X) to a methyl hydrogen muconate. (This is described in a separate paper because it raises certain interesting stereochemical points.) Moreover, Pauly *et al.* (*loc. cit.*) have made related observations in the β-methylmuconic series.

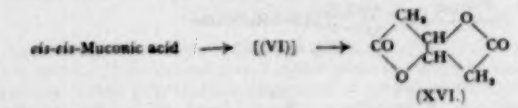
The reason for these reactions is clear: Lactonic esters such as (XII) are compounds in which an acylated hydroxyl is situated in the β-position to an electron-attracting group (carbalkoxyl). On treatment with alkaline reagents β-acyloxy-compounds of this type can undergo either normal hydrolysis (to the parent hydroxy-compounds) or *elimination* of the acyl group with the formation of an αβ-double bond. This reaction, which is now under study in these laboratories, will be further discussed in a later paper. But it is clear that the formation of double bonds by the alkaline rearrangement of lactones of this type is only a special case of a general process.

We must direct attention to the fact that the lactonic ester with the exocyclic double bond (VII; R = Me) is *not* isomerised to a methyl hydrogen muconate by means of alkoxide, being converted instead into the diester of β-ketoadipic acid (Eisner, Elvidge, and Linstead, *loc. cit.*). This is a highly interesting difference, which we attribute to the ability of (VII; R = Me) to add methoxide to form the stable enolate ion of the β-keto-ester:



This is not possible with either the isomeric unsaturated lactonic ester (X) or the saturated lactonic ester (XII). On this basis we should expect the ester of the unknown Δ^{β}-lactone (IX) to react with alkoxide in the same way as (VII; R = Me).

The evidence presented above shows that the crude product of the lactonisation of *cis-cis*-muconic acid contains both the two conjugated Δ^{α}- and Δ^{γ}-unsaturated lactones (VI) and (VII; R = H). We have no evidence that the third isomeride, the Δ^{β}-lactone (IX), is present, and in this respect the muconic acid system resembles the unsaturated diphenyl lactones investigated by Thiele and Straus (*Annalen*, 1901, **319**, 216). We have, however, found that an isomeric non-acidic material (XVI) is present as a by-product :



(XVI.)

The residues from a number of preparations on repeated crystallisation gave a compound $C_6H_4O_4$, of m. p. 128—129°. This depressed the m. p. of (VI), and was insoluble in hydrogen carbonate solution though soluble in aqueous alkali. The new compound was best prepared by prolonged treatment of *cis-cis*-muconic acid with sulphuric acid at room temperature, and could also be obtained by refluxing *cis-cis*-muconic acid with 50% sulphuric acid or by fusion of the acid, but the yields were low. It did not react with cold water, or with diazomethane under the usual conditions. Although it has not yet been examined in detail, there seems little doubt that it is the interesting dicyclic dilactone (XVI). This is in keeping with the fact that it sublimes slowly at 100° under reduced pressure. Dicyclic dilactones of similar structure (for example, the dilactone of β-acetylglutaric acid) have similar high melting points. Presumably the dilactone (XVI) has a *cis*-fusion of the rings.

Experimental.

trans-trans-Muconic acid was obtained as a chalk-like solid, m. p. 297—300°, in 29% yield from adipic acid by Ingold's procedure (*J.*, 1921, **119**, 951). Farmer (*J.*, 1932, 2531) recorded m. p. 289° (decomp.) and 300—305°, depending on the rate of heating.

Methyl trans-trans-*Muconate*.—The acid (24·8 g.) was refluxed for 80 hours with a 3% solution of hydrogen chloride in methanol (216 c.c.), and methyl *trans-trans*-muconate isolated by evaporation of the solution and crystallisation from benzene : yield, 22·5 g.; m. p. 156—157°. Esterification of the acid with ethereal diazomethane gave an identical product, and was a considerably more convenient procedure. Farmer (*loc. cit.*) reported m. p. 156° for the ester.

cis-cis-*Muconic Acid*.—The method of Böeseken and Engelberts (*loc. cit.*) was modified (cf. Grundmann, *loc. cit.*) as follows. Approximately 13% peracetic acid (785 g.) was obtained by adding a mixture of acetic anhydride (642 g.) and sulphuric acid (5 c.c.) during 9·5 hours to stirred, cooled (4—9°) 30% hydrogen peroxide (150 g.) and, after a further 3 hours, distilling the product under reduced pressure (10—15 mm.) from a bath at 30—35° into an ice-cooled receiver. The content of peracetic acid was determined by adding an excess of potassium iodide to an aliquot portion and titrating the liberated iodine. A solution of pure phenol (22·8 g.) in 13·5% peracetic acid (435 g.) was kept for 15 days in the dark. The precipitate (12 g.) was dissolved in 10% aqueous sodium hydrogen carbonate, and the solution washed with ether and stirred with charcoal. After filtration, *cis-cis*-muconic acid was precipitated with hydrochloric acid, and had m. p. 184° (Found : equiv., 71·5. Calc. for $C_6H_4O_4$: equiv., 71).

Hydrogenation.—*cis-cis*-Muconic acid (100 mg.) in ethanol was hydrogenated at room temperature and pressure in the presence of Adams's catalyst to yield adipic acid, m. p. and mixed m. p. 149—151° (hydrogen uptake : 38 c.c. at 26°/750 mm. Calc. for 2 double bonds : 35 c.c.).

Methyl cis-cis-*Muconate*.—A solution of *cis-cis*-muconic acid (0·5 g.) in methanol (60 c.c.) containing 0·5% of hydrogen chloride was kept at 5° in the dark for 48 hours. The solvent was removed under reduced pressure, and the residue washed with 10% aqueous sodium hydrogen carbonate, dried *in vacuo*, and crystallised from hexane. Methyl *cis-cis*-muconate (0·45 g.) formed massive needles, m. p. 73—73·5°. An identical product was more conveniently obtained by esterification with ethereal diazomethane. Farmer (*loc. cit.*) reported m. p. 75°, and Böeseken and Kerkhoven (*loc. cit.*) m. p. 73—74° for a methyl muconate. As we shall show in a subsequent paper, there is some doubt as to the configuration of their material.

Inversion of cis-cis- *to* trans-trans-*Muconic Acid* (cf. Grundmann, *loc. cit.*).—A solution of *cis-cis*-muconic acid (134 mg.) in alcohol (13·5 c.c.) containing a trace of iodine was irradiated with a 100-watt lamp. The precipitate, which did not further increase on continued irradiation of the solution in a quartz flask with ultra-violet light, was collected (25 mg.) and had m. p. 301° alone or in admixture with *trans-trans*-muconic acid.

Lactonisation Experiments.—(*a*) 1-G. portions of *trans-trans*-muconic acid were treated with sulphuric acid as detailed below, and the solutions were poured on crushed ice. The precipitated solid had m. p. *ca.* 300° undepressed in admixture with starting material : no other product was detected.

	H_2SO_4. Vol., c.c.	Concn., %	Temp.	Time, hrs.	Recovery of muconic acid, %.		H_2SO_4. Vol., c.c.	Concn., %	Temp.	Time, hrs.	Recovery of muconic acid, %.
(i)	30	95	23— 25°	24	100	(iv)	50	86	23— 25°	24	100
(ii)	4·5	95	120—125	0·5	82	(v)	28	86	140—165	4	70
(iii)	5	95	160—165	1	0						

(*b*) ***trans-trans*-Muconic acid** (1 g.) was recovered unchanged (m. p. and mixed m. p. 300°) in > 80% yield after being heated for 7 hours in a sealed tube at 100° with acetic acid (25 c.c.) saturated with hydrogen chloride, or after being refluxed with the same reagent (70 c.c.) for 24 hours.

(*c*) ***γ-Carboxymethyl-Δ$^{\alpha}$-butenolide*** (VI).—*cis-cis*-Muconic acid (15 g.) was suspended in a cold mixture of sulphuric acid (60 c.c.) and water (20 c.c.), and after 24 hours the solution was poured on crushed ice (200 g.). The bulk of the acid was neutralised by addition of concentrated aqueous ammonia, and the solution (just acid to Congo-red) extracted with ether for 48 hours. Evaporation of the ether gave ***γ-carboxymethyl-Δ$^{\alpha}$-butenolide*** (1 : 3-*lactone* of 3-hydroxybut-1-ene-1 : 4-dicarboxylic acid) which crystallised from benzene–ethanol as large prisms, m. p. 110·5—111·5° (12 g., 80%) (Found: C, 51·1; H, 4·8%; hydrolysis-equiv., 71. $C_5H_4O_4$ requires C, 50·7; H, 4·25%; equiv., 71). Light absorption in dry dioxan: end absorption only, $\epsilon = 1420$ at 2260 A. [*cf.* the isomeric lactonic acid (Part III)]. Its *methyl* ester (X) was prepared by treating the recrystallised lactonic acid (VI) (8 g.) with an excess of ethereal diazomethane; the solution was distilled, finally under reduced pressure, to yield an oil, b. p. 154°/12 mm., which rapidly solidified. Crystallisation was effected by cooling an ether solution with solid carbon dioxide; the ester formed a fine white powder, m. p. 30·5—31° (Found: C, 54·0; H, 5·3%; hydrolysis-equiv., 78·1. $C_7H_8O_4$ requires C, 53·9; H, 5·1%; equiv., 78).

γ-Carbomethoxymethylenebutanolide (***γ-Carbomethoxymethylene-γ-butyrolactone***) (VII; R = Me).—Crude lactonic acid (12·7 g.; direct from cyclisation of *cis-cis*-muconic acid) was treated with an excess of ethereal diazomethane, and the solution filtered and distilled, eventually under reduced pressure. After a small forerun, the main fraction was collected at 126—134°/1 mm. as a mixture (10·2 g.) of liquid and solid. The latter was collected and washed with ether; yield, 0·9 g. After crystallisation from ether–light petroleum (b. p. 40—60°) the material had m. p. 108—109° (Found: hydrolysis-equiv., 77·4. Calc. for $C_7H_8O_4$: equiv., 78) and was identical with γ-carbomethoxymethylenebutanolide, m. p. 110° (Eisner, Elvidge, and Linstead, *J.*, 1950, 2223).

Colour Reactions of the Lactonic Esters and Acids.—The procedures have been outlined previously (Kuehl, Linstead, and Orkin, *J.*, 1950, 2213).

Légal reaction:	pH 11.	pH 13.
γ-Carbomethoxymethyl-Δ$^{\alpha}$-butenolide (X)	Light pink, fading slowly	Red, fading to yellow
γ-Carbomethoxymethylenebutanolide (VII; R = Me)	Darker pink	Darker red

Tollens's reagent:	
γ-Carboxymethyl-Δ$^{\alpha}$-butenolide (VI)	Instantaneous ppt. of silver
(X)	" " "
γ-Carboxymethylenebutanolide (VII; R = H)	Negative
(VII; R = Me)	"

Ammoniacal silver nitrate:	
(VI)	Slight ppt. of silver after 2 hours
(X)	" " "
(VII; R = H)	Negative
(VII; R = Me)	"

2 : 6-Dichlorophenolindophenol:	pH 11.	pH 13.
(X)	Fades to green	Fades rapidly to greenish-yellow
(VII; R = Me)	Fades very slowly (4 hours) to green	Reddish-brown after 4 hours

The last red colour denoted that the solution had become acid, owing to opening of the lactone ring.

Alkaline Hydrolysis of γ-Carboxymethyl-Δ$^{\alpha}$-butenolide.—A solution of the lactonic acid (0·1 g.) in 10% sodium hydroxide (5 c.c.) was refluxed for 20 minutes, then acidified with hydrochloric acid, clarified, and treated with semicarbazide hydrochloride (0·15 g.) in water (7 c.c.) containing sodium acetate (0·3 g.). Overnight, crystals of lævulic acid semicarbazone separated (35 mg.), m. p. and mixed m. p. 184°.

Oxidation of γ-Carboxymethyl-Δ$^{\alpha}$-butenolide.—A solution of the lactonic acid (1·5 g.) and sodium carbonate (0·56 g.) in water (10 c.c.) was cooled in ice and stirred whilst potassium permanganate (3·35 g., 3 atoms of O) in water (500 c.c.) was added during 10 hours. Manganese dioxide was filtered off, and the filtrate made acid to Congo-red with hydrochloric acid and extracted with ether for 40 hours. Evaporation of the ether gave a residue which was dissolved in hot water (10 c.c.) and treated with a slight excess of 10% calcium chloride solution. The precipitate was collected, washed with boiling water, then treated with hydrochloric acid. By extraction with ether for 40 hours colourless crystals (450 mg., 47%) were obtained which had m. p. 100° alone and in admixture with oxalic acid dihydrate. The aqueous solution from the first ether-extraction was evaporated to 10 c.c., neutralised to litmus with ammonia, and treated hot with a small excess of 10% aqueous lead acetate. The precipitate was

washed with boiling water, then decomposed in water with hydrogen sulphide, and the filtrate evaporated to dryness to yield a white solid (100 mg., 7%) which had m. p. 124—126° undepressed by malic acid (m. p. 130°).

Reactivity of γ-Carboxymethyl-Δ$^{\alpha}$*-butenolide.*—(i) The lactonic acid was unaffected by being kept at room temperature with water or dilute acids, and was recovered unchanged (m. p. and mixed m. p. 109—110°) after being refluxed for 2·5 hours with dry methanol containing a trace of hydrogen chloride. (ii) The lactonic acid (500 mg.) was dissolved in 0·1*N*-potassium hydroxide (70·4 c.c., 2 equivs.), and after 18 hours at room temperature the yellowish solution was acidified to Congo-red with dilute sulphuric acid and extracted with ether for 16 hours. The solid obtained by evaporation of the ether was separated from oil and crystallised from anethole to give prisms, m. p. 110° undepressed by the lactonic acid (VI). The oil was treated with semicarbazide hydrochloride (0·2 g.), sodium acetate (0·2 g.), and water (2 c.c.), and the white crystals which formed were recrystallised from ethanol: they then had m. p. 184° undepressed by lævulic acid semicarbazone. (iii) The lactonic acid methyl ester (X) (0·8 g.) and aniline (0·6 g.) were dissolved together in a minimum of ethanol. After 3 days at room temperature the solvent was evaporated to leave a residue which failed to crystallise. By distillation, aniline (0·5 g., 83%), b. p. 180—182°, was recovered.

Hydrogenation of γ-Carboxymethyl-Δ$^{\alpha}$*-butenolide: The γ-Lactone of β′-Hydroxyadipic Acid.*—The unsaturated lactonic acid (VI) (0·65 g.) in acetic acid (25 c.c.) was hydrogenated at room temperature and pressure in the presence of Adams's catalyst (36 mg.). Hydrogen uptake (Found: 122 c.c. at 25°/760 mm. Calc. for 1 double bond: 112 c.c.) was complete in 10 minutes. The catalyst was removed, and the filtrate evaporated to yield an oil which slowly solidified. From benzene or ether–hexane, the *γ-lactone* (XI) of β′-hydroxyadipic acid slowly crystallised, m. p. 60—61° (Found: C, 50·5; H, 5·5. $C_6H_8O_4$ requires C, 50·0; H, 5·6%). On rapid titration of this compound (72·4 mg.) in water (5 c.c.) to the phenolphthalein end-point 4·96 c.c. of 0·105*N*-sodium hydroxide were consumed ($C_6H_8O_4$,CO_2H requires 4·55 c.c.); an excess of alkali was then added, the solution heated on the steam-bath for 5 minutes and back-titrated with standard acid (Found: hydrolysis-equiv., 71·5. $C_6H_8O_4$ requires equiv., 72).

Methyl ester (XII). The unsaturated lactonic ester (X) (3·43 g.) in 95% alcohol (45 c.c.) was hydrogenated at room temperature and pressure in the presence of Adams's catalyst (69 mg.). The uptake of hydrogen (570 c.c. at 27°/758 mm. Calc. for 1 double bond: 596 c.c.) was complete in 30 minutes. After filtration, the solution was distilled, finally under reduced pressure, to give the *methyl* ester (XII) as a colourless liquid, b. p. 125°/2 mm. (Found: C, 52·6; H, 6·5. $C_7H_{10}O_4$ requires C, 53·15; H, 6·3%).

Hydrolysis of the Methyl Ester (XII).—(a) *With acid.* The ester (1·5 g.) was heated under reflux with 10% hydrochloric acid (25 c.c.) for 4 hours, and the solution concentrated to small bulk in a vacuum-desiccator. The residue solidified on treatment with ether. Crystallisation from benzene afforded (XI), m. p. and mixed m. p. 60—61°.

(b) *With alkali.* A solution of the ester (0·5 g.) in alcohol was refluxed for 3 hours with 10% aqueous sodium hydrogen carbonate (10 c.c.). Acidification of the cooled solution with 10% hydrochloric acid precipitated a solid (0·39 g.) which, recrystallised from hot water, had m. p. 190—191° alone and when mixed with an authentic specimen of *trans*-Δ$^{\alpha}$-dihydromuconic acid (XIII) (see below) (Found: C, 50·1; H, 6·1%; equiv., 72·8. Calc. for $C_6H_8O_4$: C, 50·0; H, 5·6%; equiv., 72). Hydrogenation of this product (117 mg.) in 95% alcohol (25 c.c.) in the presence of platinum-black gave adipic acid, m. p. and mixed m. p. 146—148° (Hydrogen uptake: 20 c.c. at 27°/757 mm. Calc. for 1 double bond: 20 c.c.).

The Action of Sodium Methoxide on γ-Carbomethoxymethylbutanolide (XII).—The ester (0·8 g.) was treated for 20 minutes at room temperature with anhydrous methanolic sodium methoxide (2·2 c.c.; 2·28*N*.). The solvent was evaporated, the residue taken up in water (10 c.c.), and the solution acidified with 10% hydrochloric acid. An oil separated which was isolated with ether; crystallisation then occurred. From ether–light petroleum (b. p. 40—60°) slender needles (650 mg.), m. p. 40—41°, of *methyl 5-carboxy-trans-pent-2-enoate** (XIV) separated (Found: C, 53·6; H, 6·3%; equiv., 158; hydrolysis-equiv., 78·3. $C_7H_{10}O_4$ requires C, 53·15; H, 6·3%; equivs., 158, 79). The solution from the saponification of this ester (115 mg.) was acidified and concentrated *in vacuo*. *trans*-Δ$^{\alpha}$-Dihydromuconic acid separated (90 mg.), m. p. 188—190° and mixed m. p. 189—191°.

Oxidation of the Methyl Hydrogen Dihydromuconate (*Methyl 5-Carboxy-trans-pent-2-enoate**) (XIV).—The half-ester (350 mg.) was dissolved in water (5 c.c.) by addition of a small excess of 10% sodium carbonate, and to the solution at 0° 3% aqueous potassium permanganate (30 c.c.) was added dropwise. Excess of permanganate was decomposed with sodium hydrogen sulphite, the manganese dioxide filtered off and washed with hot water (30 c.c.), and the combined filtrate and washings were acidified with 10% hydrochloric acid and extracted with ether for 44 hours. Evaporation of the ether to small bulk afforded a crystalline solid (170 mg., 65%), m. p. 178—180° undepressed by succinic acid. The mother-liquors were acidified with dilute sulphuric acid and diluted with water to 100 c.c. Oxalic acid was detected and determined by titration of a portion (50 c.c.) with 0·055*N*-potassium permanganate (Consumption: 45·0 c.c. Calc. for 100% yield of oxalic acid: 40·0 c.c.).

[With Dexter B. Pattison.]

The Methyl Hydrogen Dihydromuconate (*5-Carbomethoxypent-2-enoic Acid**) (XV).—(a) *Preparation by the Doebner reaction.* A mixture of β-carbomethoxypropaldehyde (15 g.) (Johnson, Linstead, and Whetstone, *J.*, 1950, 2219), malonic acid (15·4 g.), and dry pyridine (16 c.c.) was kept at room temperature for 3 days, then heated on the steam-bath overnight. Water was added, and the solution acidified with

* Geneva numbering.

hydrochloric acid and extracted (5 times) with ether. The extract was shaken with sodium hydrogen carbonate solution, and the aqueous layer washed with ether, acidified, and extracted with ether. Evaporation of the latter afforded 5-carbomethoxy-*trans*-pent-2-enoic acid[9] (12·6 g.; 62%) which crystallised from light petroleum (b. p. 60—80°) and then had m. p. 61° (Found: C, 52·3; H, 6·55%; equiv., 157·5. Calc. for $C_7H_{10}O_4$: C, 53·15; H, 6·3%; equiv., 158). Farmer and Hughes (*J.*, 1924, 1929, 1938) gave m. p. 60°.

(b) *Hydrolysis to* trans-Δ$^{\alpha}$-*dihydromuconic Acid* (XIII). The preceding half-ester was heated under reflux for 15 minutes with aqueous sodium hydroxide (1·5 equivs.), and the solution acidified and extracted with ether. The ether was dried (Na_2SO_4) and evaporated, and the residue of *trans*-Δ$^{\alpha}$-dihydromuconic acid crystallised from water; it had m. p. 191—193°.

(c) *Oxidation.* A stirred solution of the methyl hydrogen dihydromuconate (XV) (2 g.) in water (300 c.c.) containing sodium hydrogen carbonate (1·1 g.) was treated at 0° during 2 hours with a slight excess of 2% potassium permanganate solution. Excess of permanganate was decomposed with aqueous formaldehyde, and the filtrate from the manganese dioxide acidified with hydrochloric acid and extracted with ether (5 × 100 c.c.). Acidic material present in the ether was purified by passage through aqueous sodium hydrogen carbonate and recrystallisation from carbon disulphide. The methyl hydrogen succinate (0·21 g., 12·5%) formed plates, m. p. and mixed m. p. 56—57°.

(d) *Hydrogenation.* Reduction of the methyl hydrogen dihydromuconate (XV) (2·3 g.) in acetic acid (8 c.c.) with hydrogen and Adams's catalyst (27 mg.) was complete in 15 minutes. The solution was filtered, boiled with concentrated hydrochloric acid, and evaporated, and the residue extracted with ether. The latter was dried (Na_2SO_4) and evaporated to give crystals (1·7 g., 80%), m. p. 150—151° undepressed by adipic acid.

[With HAROLD BAER.]

3 : 7-*Dikeio*-2 : 6-*dioxa*bicyclo[3 : 3 : 0]*octane* (*Butanolido-*β*-*γ*′-*β*′-butanolide*) (XVI).—(i) A solution of *cis-cis*-muconic acid (6 g.) in a mixture of sulphuric acid (30 c.c.) and water (10 c.c.) was kept for 6 weeks, then neutralised (to Congo-red) at 0° with ammonia. Water was added to dissolve the precipitate, and the solution extracted with ether for 24 hours. On cooling the ether, a solid separated (2·4 g.), m. p. 118—121°. Repeated crystallisation from ether or anisole afforded the *diketone*, m. p. 128—129° (Found: C, 50·6; H, 4·2. $C_8H_8O_4$ requires C, 50·7; H, 4·25%), which was insoluble in aqueous sodium hydrogen carbonate. A mixture with γ-carboxymethyl-Δ$^{\alpha}$-butenolide (m. p. 110°) had m. p. 89—92°. (ii) *cis-cis*-Muconic acid was heated at 200°, then cooled, and the red gel-like mass taken up in alcohol. After filtration and evaporation of the solution, crystallisation slowly occurred. From alcohol (charcoal), by concentration, the cyclic diketone crystallised, having m. p. and mixed m. p. 125—126°. On titration at room temperature the dilactone consumed only 1 equiv. of sodium hydroxide; at 50°, 2 equivs. were rapidly taken up.

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462. *The Third Isomeric* (cis-trans-)*Muconic Acid.*

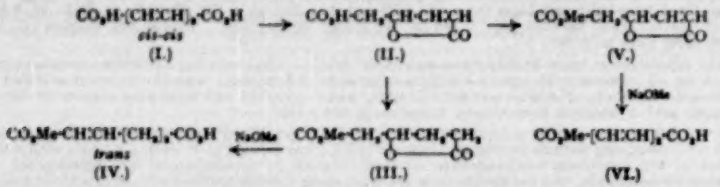
By J. A. ELVIDGE, R. P. LINSTEAD, PETER SIMS, and (in part) B. A. ORKIN.

Isomerisation of γ-carbomethoxymethyl-Δ$^{\alpha}$-butenolide (V) with sodium methoxide in methanol affords a methyl hydrogen muconate (VI) which has a *trans-cis*-configuration. Hydrolysis with alkali gives the corresponding *trans-cis*-muconic acid (VII), and reaction with diazomethane yields the methyl *cis-trans*-muconate (VIII). The *cis-cis*- and *cis-trans*-forms of muconic acid show a remarkable similarity which has hitherto concealed the existence of the new isomeride. The m. p.s of the free acids are nearly the same and their dimethyl esters likewise have almost identical melting points, although those of the benzhydryl esters differ from one another. The three pairs of compounds show distinct depressions of melting point although this is not large for the free acids. The ultra-violet and infra-red light absorption characteristics of the three muconic acids and their esters are recorded. The stereochemical stabilities of the *cis-cis*- and *cis-trans*-muconic acids have been studied. *cis-cis*-Muconic acid is quantitatively inverted to *cis-trans*-muconic acid merely on boiling with water. The significance of this observation in relation to results obtained by earlier workers in the field is pointed out.

WE have recently described the lactonisation of *cis-cis*-muconic acid (I) (Elvidge, Linstead, Orkin, Sims, Baer, and Pattison, *J.*, 1950, 2228). The product (II) on hydrogenation and esterification gave the saturated lactonic ester, γ-carbomethoxymethylbutanolide (δ-carbomethoxyvalerolactone) (III). This could readily be isomerised by means of sodium methoxide to methyl hydrogen *trans*-Δ$^{\alpha}$-dihydromuconate (but-1-ene-1 : 4-dicarboxylate) (IV).

This isomerisation, together with those observed by Pauly and his co-workers on the higher homologue (*Annalen*, 1914, **403**, 119; 1918, **416**, 1), made it appear probable that the *unsaturated* lactonic ester (V) would rearrange similarly to an acid ester of muconic acid (VI). Moreover,

an interesting stereochemical point arose. In the ring-opening of (III) to (IV) a *trans*-Δ$^{\alpha}$-double bond is formed. This falls into line with recent work on the alkaline fission of β-acyloxy-



acids and esters. It has been found, for example, that acyl derivatives of β-hydroxybutyric acid yield *trans*-crotonic acid with alkaline reagents (Linstead, Owen, and Webb, unpublished observations). It thus appeared probable that the substituents about the *new* double bond, formed in the ring opening (V) ⟶ (VI), would have the *trans*-configuration, whereas the double bond pre-existing in the ring would be *cis*. This would mean that the product would be a derivative of a new *cis-trans*-muconic acid and differing from the known isomerides melting at about 187° (*cis-cis*) and 300° (*trans-trans*).

Treatment of the unsaturated lactonic ester with sodium methoxide in methanol gave the expected methyl hydrogen muconate (VI) in about 30% yield. From the mother-liquors lævulic acid [presumably derived from (V) *via* hydrolysis to β-ketoadipic acid] was isolated as the 2 : 4-dinitrophenylhydrazone. Over a platinum catalyst (VI) took up 2 mols. of hydrogen and gave a product which yielded adipic acid on acid hydrolysis. Hydrolysis of (VI) gave a muconic acid (VII), m. p. 184°, which in admixture with *cis-cis*-muconic acid (m. p. 184°; made by oxidation of phenol with peracetic acid) melted at 180—184°. The melting points and mixed melting point of these acids vary with the rate of heating in a manner described later. Esterification either of the muconic acid or of the half-ester (VI) with diazomethane yielded a dimethyl ester with a melting point (75°) almost identical with that (73·5°) of the *cis-cis*-dimethyl ester. However, a mixture of the two esters gave an unmistakable depression of some 15—20°, so that clearly the ester of m. p. 75°, derived from the lactone, was not identical with dimethyl *cis-cis*-muconate; nor was it identical with dimethyl *trans-trans*-muconate which melts at 157°. On the other hand, the analytical values, including methoxyl determination, gave good agreement with those required for a dimethyl muconate, and the ultra-violet absorption spectrum also agreed.

It thus appeared that, in spite of the similarities, the compounds prepared from the lactonic ester (V) did in fact belong to a new geometrically isomeric series. This was confirmed by an examination of the benzhydryl esters. The two known muconic acids and the new isomeride, on treatment with diphenyldiazomethane, gave three distinct esters, with m. p.s 157° (*cis-cis*), 191° (*trans-trans*), and 143·5° (from the new acid). These gave correct analytical figures and each depressed the m. p. of the other two.

Although the existence of a third muconic acid was by now certain, we were perplexed by a lack of reproducibility in the results. Thus the following series of conversions was carried out several times by three separate workers :

Phenol ⟶ *cis-cis*-acid (I) ⟶ (II) ⟶ (V) ⟶ (VI)

and the dimethyl esters were prepared from (I) and (VI). Generally, two distinct esters were formed, giving a m. p. depression of about 20° as described above, but on two or three occasions the esters obtained were identical, which made it appear at first sight that sometimes the inversion failed to occur during the changes (I) ⟶ (VI). Subsequently the following reactions were carried out, which, although apparently puzzling, actually provided the clue to the problem. A sample of muconic acid, " A," freshly made from phenol, was converted by diphenyldiazomethane into the new benzhydryl ester of m. p. 143·5° instead of into the expected *cis-cis*-isomeride of m. p. 157°. The ester was hydrolysed and the acid so obtained, " B," together with the starting material " A " were converted into dimethyl esters which were compared with the authentic esters, m. p. 73·5° and m. p. 75° respectively, of the *cis-cis*- and of the " new " acid. It was found that A and B were identical with one another and with the new acid : their esters and the new ester had the same m. p.s and mixed m. p.s, but gave a large depression with the *cis-cis* ester. *Thus the explanation of the anomaly was not that the inversion*

(I) ⟶ (VI) was *unreliable but that the starting material had sometimes become inverted in the course of its preparation.*

We accordingly prepared some ***cis-cis*-muconic acid** under carefully controlled conditions. All use of heat was avoided and access to light was kept to the minimum. The acid was then subjected to various purification procedures, and the various samples of the acid were identified by conversion into methyl or benzhydryl esters and comparison with authentic material. It was found that the *cis-cis*-acid could be crystallised unchanged from boiling methanol or ethanol and was unaffected by dissolution in alkali and liberation with mineral acid. The solid *cis-cis*-acid could be kept at 100° for 4 hours without change, and was unchanged by exposure to daylight (4—5 weeks). Moreover, solutions of the acid in ethanol or alkali were unchanged by exposure to ultra-violet light for 30 minutes and 3 minutes, respectively. The sodium salt was stable to boiling water, at least for short periods. However, crystallisation of the free acid from boiling water was sufficient to bring about rapid and complete inversion. A full explanation was thus provided for the earlier lack of reproducibility: some samples of acid had been crystallised from boiling water and had thus been inverted; others had not. Incidentally, crystallisation from boiling water had been used by previous workers for the purification of the *cis-cis*-acid: we return to this point later.

It is thus established that the muconic acid formed by the oxidation of phenol can be converted into an isomeride by boiling water or, indirectly, through the lactonic acid (II). The new compound must be a muconic acid because it is hydrogenated to adipic acid and converted into *trans-trans*-muconic acid when an aqueous solution containing a trace of iodine is irradiated by ultra-violet light. The muconic acid structure is also supported by the ultra-violet and infra-red spectra. It seems very probable that the oxidation product of phenol has the *cis-cis*-configuration. The assignment of the *trans-trans*-configuration to the long-known acid of m. p. 300° appears established (see summary by Elvidge, Linstead, Orkin, Sims, Baer, and Pattison, *loc. cit.*). This leaves the *cis-trans*-configuration for the new acid and this is supported (i) by the argument advanced earlier, and (ii) by the fact that the new acid is intermediate in stability between the other two isomerides, being readily formed from one in boiling water and converted into the other by ultra-violet light. The muconic acids and their esters provide a further interesting example of the isolation in all three possible stereochemical forms of a 1 : 3-butadiene system. Farmer (*J.*, 1923, **123**, 2531) has described the three forms of ethyl αα′-dibromomuconate, and the three stereoisomers of diphenylbutadiene have been prepared and investigated by Strauss and Müller (*Annalen*, 1905, **342**, 190) and by Pinckard, Wille, and Zechmeister (*J. Amer. Chem. Soc.*, 1948, **70**, 1938).

Because of the general similarity between the *cis-cis*- and *cis-trans*-muconic acids a number of their properties have been carefully determined. Analytically pure *cis-cis*-acid is best obtained by crystallisation from ethanol, from which it separates as stout prisms or rhombs. The *cis-trans*-acid, prepared by either of the methods already described, separates from ethanol or water in long prismatic needles. The melting point and mixed melting point, determined in the usual way, have already been described. If the specimens are placed in a bath at 165° and the temperature raised rapidly (10° per minute), then differences between the two acids are more apparent, the *cis-cis* melting at 194—195°, the *cis-trans* at 190—191°, and a mixture at 180—185° or even lower.

The properties of the three muconic acids are described in detail in the experimental section: light absorption data are recorded in the table (p. 2238).

It is to be noted that the positions of the ultra-violet absorption maxima are the same for each stereoisomer. In the carotenoids it has been observed (Zechmeister, *Chem. Rev.*, 1944, **34**, 267) that a single *trans*- to *cis*-inversion shifts the position of the main absorption band by ~75 A. toward shorter wave-lengths. In the diphenylbutadienes the corresponding shift is 140—150 A. (Pinckard, Wille, and Zechmeister, *loc. cit.*) which is close to that observed for the change *trans*- to *cis*-stilbene. Methyl fumarate and maleate show absorption maxima at 2087 A. ($\varepsilon = 32{,}180$) and 1927 A. ($\varepsilon = 28{,}290$), respectively (Sörensen, *Annalen*, 1941, **546**, 57), the shift in this case being 160 A. In all these examples, however, the *trans*-forms absorb the more intensely.

Further points of interest arise from an examination of scale models (constructed on covalent atomic radii). The occurrence of resonance in conjugated systems and the concomitant requisite of a planar configuration are current conceptions which imply that there are in general only two allowable steric arrangements about each formal single bond within a conjugated system: these possible orientations are designated as *s-cis* and *s-trans*. Models show that with an *s-cis*-orientation (about the central single bond) steric interference with a planar configuration occurs in both the *cis-cis*- and the *cis-trans*-muconic acid and particularly their

Light absorption data for the muconic acids and esters.

Infra-red absorption : characteristic frequencies (cm.$^{-1}$). (Measurements by Mr. J. L. Hales, Chemical Research Laboratory, Teddington.)

	Acids (paste in " Nujol ").	Methyl esters (in CCl_4).		Acids (paste in " Nujol ").	Methyl esters (in CCl_4).
cis-cis	1250	1370	*cis-trans*	890	1310
	830	900		760	1095
		830			880
			trans-trans	1020	—
				870	—

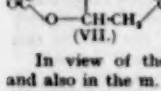
Ultra-violet absorption (the isomers are stable under the conditions of the determinations, see Experimental).

	Acids (in 0·1*N*-NaOH).		Methyl esters (in EtOH).		Benzhydryl esters (in EtOH).	
	$\lambda_{max.}$ A.	ε.	$\lambda_{max.}$ A.	ε.	$\lambda_{max.}$ A.	ε.
cis-cis	2510	15,600	2590	26,400	2650	30,400
	2580	17,000	2650	23,800		
	2640	15,300				
cis-trans	2510	23,400	2600	29,800	2660	33,200
	2590	25,600	2660	28,900		
	2650	23,400				
trans-trans	2510	25,600	2590	36,700	2660	35,600
	2590	29,100	2650	34,000		
	2640	25,600				

esters. Intramolecular interference effects are absent from the *s-trans*-forms, so that an *s-trans*-configuration for the *cis-cis*- and the *cis-trans*-isomer is strongly indicated. (Indeed, it is now generally conceded that the most elongated form of a conjugated system is the most stable.) The ultra-violet light absorption data are not inconsistent with such a view. The three muconic acids have been titrated electrometrically. All are strong acids and give closely similar titration curves. This therefore does not provide a method for the identification of the isomerides but it gives evidence which falls into line with the idea developed above that the *cis-cis*- and *cis-trans*-acids have extended configurations. On this basis the spacing between the carboxyl groups and hence the acid strengths would be roughly the same. It is noteworthy that the scale models indicate that there should be no difference in the ease of lactonisation of the *cis-cis*- and *cis-trans*-muconic acids, provided that they both exist in the *s-trans*-form. No difference has been detected experimentally.

Grundmann (*Ber.*, 1936, **69**, 1755) observed the iodine-catalysed photochemical inversion of *cis-cis*- to *trans-trans*-muconic acid and we have shown the change *cis-trans* ⟶ *trans-trans* occurs under the same conditions. It seemed possible that in comparative experiments involving the irradiation of aqueous solutions of the *cis-cis*- and *cis-trans*-acids there might be some difference in the rate of precipitation of the *trans-trans*-acid. None could, however, be detected. The simplest explanation is that the photochemical change *cis-cis* ⟶ *cis-trans* is faster than the second stage, *cis-trans* ⟶ *trans-trans*, although this is in truth very rapid.

The rapid and complete inversion of *cis-cis*-muconic acid to the *cis-trans*-isomer in boiling water is remarkable, the more so in view of the stability of the *cis-cis*-form under other conditions where a slow isomerisation might have been expected. It is unlikely that the inversion proceeds *via* the lactonic acid (II) : evidence that a lactone can scarcely be an *intermediate* in the inversion was provided by the production of the dilactone (VII) on prolonged boiling of *cis-cis*-muconic acid with water. The dilactone was more readily formed from *cis-cis*-muconic acid by the action of boiling dilute hydrochloric acid and in this reaction the lactonic acid (II) may well be an intermediate. Under these conditions the formation of (VII) occurred even more easily from (II) than from *cis-cis*-muconic acid.



(VII.)

In view of the similarity between the m. p.s of *cis-cis*- and *cis-trans*-muconic acids, and also in the m. p.s of their methyl esters, it is not surprising that previous workers in the field failed to observe the inversion which accompanies the crystallisation of *cis-cis*-muconic acid from boiling water. The specimens of muconic acid, m. p. 187°, which Farmer (*J.*, 1923, **123**, 2531) (see also Farmer and Duffin, *J.*, 1927, 402), Böeseken (*Proc. Acad. Sci. Amsterdam*, 1929, **32**, 1043), and Böeseken and Kerkhoven (*Rec. Trav. chim.*, 1932, **51**, 964) described and regarded as the *cis-cis*-isomer were in each case crystallised from water. As a consequence, it is highly probable that the purified material obtained by these workers was in fact the *cis-*

trans-isomer, although there is little doubt that the crude product of the oxidation of phenol which Böeseken and Kerkhoven obtained was *cis-cis*-muconic acid. It is also possible that the conclusions which the last authors drew from their experiments on the oxidation of their muconic acid are not valid since it seems very likely that recrystallised material was employed. The true stereochemical identity of the methyl muconate of m. p. 75° prepared by Farmer (*loc. cit.*) and reinvestigated by Böeseken and Kerkhoven also remains uncertain. Repetition of the work of Farmer and of Böeseken will be necessary to clear up these points.

Experimental.

(M. p.s marked * were taken from a bath at 165°, with the temperature rising at 10°/minute. Other m. p.s were determined normally.)

† *The Action of Sodium Methoxide on γ-Carbomethoxymethyl-Δ*$^{\alpha}$*-butenolide* (*3-Hydroxy-4-carbomethoxybut-1-ene-1-carboxylic Acid Lactone*) (V); *Formation of a Methyl Hydrogen* trans-cis-*Muconate*.—The lactonic ester (Elvidge, Linstead, Orkin, Sims, Baer, and Pattison, *loc. cit.*) (4·5 g.) in dry methanol (10 c.c.) was kept for 30 minutes with sodium methoxide in methanol (12 c.c.; 2·5*N*.). The solvent was then evaporated under reduced pressure, the residue taken up in water, and the solution acidified to Congo-red with concentrated hydrochloric acid. An oil separated which rapidly solidified. From benzene, the *methyl hydrogen* trans-cis-*muconate* (VI) formed needles (1·5 g.; 32%), m. p. 101° (Found: C, 54·25; H, 5·4; OMe, 19·7%; equiv., 155·3. $C_7H_8O_4$ requires C, 53·9; H, 5·2; OMe, 19·9%; equiv., 156).

In another experiment the lactonic ester (1·4 g.) and sodium methoxide gave methyl hydrogen *trans-cis*-muconate (0·4 g.) in 29% yield. The filtrate was kept for 10 days, then extracted with ether, and the ethereal solution evaporated. Treatment of the residue in ethanol with 2 : 4-dinitrophenylhydrazine in dilute hydrochloric acid gave an orange precipitate (0·9 g., 35%) which crystallised from chloroform to give orange needles of lævulic acid 2 : 4-dinitrophenylhydrazone, m. p. 205° and mixed m. p. 205—206°. Treatment of the derivative (0·1 g.) with ethereal diazomethane afforded orange needles (from ethanol) of methyl lævulate 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 141°.

† cis-trans-*Muconic Acid*.—The foregoing half-ester (250 mg.) was heated with 10% aqueous sodium hydroxide (2 c.c.) on the steam-bath for 10 minutes. The solution was cooled and acidified with hydrochloric acid, and the precipitate crystallised from hot water to give prismatic needles (200 mg., 90%), m. p. 190—191°* of cis-trans-*muconic acid* (Found: C, 51·0; H, 4·45%; equiv., 70·8. $C_6H_6O_4$ requires C, 50·7; H, 4·25%; equiv., 71). For mixed m. p. of this and the *cis-cis*-acid, see p. 2237.

Hydrogenation of *cis-trans*-muconic acid (100 mg.) in ethanol in the presence of Adams's catalyst (hydrogen uptake: 35·5 c.c. at 21°/765 mm. Calc. for 2 double bonds: 33·9 c.c.) gave adipic acid, m. p. and mixed m. p. 150°.

† *Methyl* cis-trans-*Muconate*.—(*a*) Methyl hydrogen *trans-cis*-muconate (150 mg.) was treated with a small excess of diazomethane in ether, the solution evaporated under reduced pressure, and the residue crystallised from aqueous methanol. *Methyl* cis-trans-*muconate* (yield almost quantitative) formed needles, m. p. 75° (Found: C, 56·8, 56·5; H, 6·3, 6·0; OMe, 37·1%; hydrolysis-equiv., 86·8. $C_8H_{10}O_4$ requires C, 56·5; H, 5·9; OMe, 36·5%; equiv., 85). A mixture with methyl *cis-cis*-muconate (m. p. 73·5°) had m. p. 50—55°.

(*b*) Reaction of *cis-trans*-muconic acid (100 mg.) with ethereal diazomethane similarly afforded methyl *cis-trans*-muconate (needles from aqueous methanol), m. p. and mixed m. p. 75°, but depressed by methyl *cis-cis*-muconate.

Lactonisation of cis-trans-*Muconic Acid*.—A suspension of the acid (1 g.) in 75% sulphuric acid (5 c.c.) was kept for 24 hours and poured on crushed ice (20 g.), and the bulk of the acid neutralised with concentrated ammonia solution. The solution (just acid to Congo-red) was extracted with ether for 40 hours, the extract evaporated, and the crystalline residue recrystallised from benzene–ethanol. γ-Carboxymethyl-Δ$^{\alpha}$-butenolide separated as prisms, m. p. 110° alone or on admixture with material prepared from the *cis-cis*-acid.

cis-cis-Muconic acid was prepared as described by Elvidge, Linstead, Orkin, Sims, Baer, and Pattison (*loc. cit.*) except that particular care was taken to avoid the application of heat at any stage, and access of light was kept to an absolute minimum. The crude acid had m. p. 179—183°; treatment of a portion (0·5 g.) with diazomethane in ether gave a quantitative yield of methyl *cis-cis*-muconate, m. p. 73° (from aqueous methanol) depressed to 50—55° by methyl *cis-trans*-muconate. The crude acid (0·5-g. portions) did not undergo inversion on crystallisation from methanol or ethanol; from ethanol, cis-cis-*muconic acid* separated as prisms or rhombs (0·2 g.), m. p. 194—195°* (Found: C, 51·05; H, 4·4%; equiv., 70·9. $C_6H_6O_4$ requires C, 50·7; H, 4·25%; equiv., 71).

Methyl cis-cis-*muconate* was obtained from both the crude and the preceding purified *cis-cis*-acid with diazomethane in ether, and crystallised from aqueous methanol and from hexane as needles, m. p. 73·5° (Found: C, 56·15; H, 5·9; OMe, 36·2. $C_8H_{10}O_4$ requires C, 56·5; H, 5·9; OMe, 36·5%).

Dependence of M. P. upon Stereochemical Purity.—The m. p.s of known mixtures of methyl *cis-cis*- and *cis-trans*-muconates were: 80 : 20, m. p. 50—55°; 85 : 15, 60—63°; 95 : 5, 67—69°.

trans-trans-Muconic acid (Ingold, *J.*, 1921, **119**, 951) was recrystallised from a large volume of boiling water and thus obtained as minute prisms, m. p. 301° (Found: equiv., 70·3. Calc. for $C_6H_6O_4$: equiv., 71). Its dimethyl ester, prepared from the acid and diazomethane, crystallised from ethanol as needles, m. p. 157°.

† With B. A. Orkin, Harvard University.

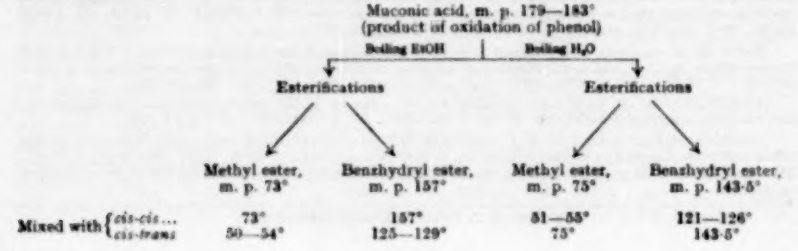
Benzhydryl Muconates.—Diphenyldiazomethane, prepared by shaking benzophenone hydrazone (2·2 g.) with yellow mercuric oxide (2·28 g.) in light petroleum (b. p. 40—60°) (20 c.c.) for 8 hours (Staudinger, Anthes, and Pfenniger, *Ber.*, 1916, **49**, 1932), was dissolved in ether (30 c.c.). To a portion (10 c.c.) *trans-trans*-muconic acid (0·2 g.) and methanol (2 c.c.) were added, and the mixture was kept in the dark for several hours. Evaporation of the ether under reduced pressure and crystallisation of the residue from methanol gave needles, m. p. 191°, of *benzhydryl* trans-trans-*muconate* (Found: C, 80·95; H, 5·7. $C_{38}H_{34}O_4$ requires C, 81·0; H, 5·5%). Similarly prepared and crystallised were *benzhydryl* cis-trans-*muconate*, needles, m. p. 143·5° (Found: C, 80·9; H, 5·7%), and *benzhydryl* cis-cis-*muconate*, needles, m. p. 157° (Found: C, 80·9; H, 5·8%). Mixtures of the three pairs of esters showed m. p. depressions of 20—30°.

Hydrolysis of Esters.—(i) After being kept overnight with concentrated hydrochloric acid (1 c.c.), benzhydryl *cis-trans*-muconate (50 mg.) was recovered unchanged (40 mg.; m. p. and mixed m. p. 143·5°). (ii) Benzhydryl *cis-trans*-muconate (0·5 g.) was refluxed with 10% aqueous sodium hydroxide (5 c.c.) for 8 hours, and the mixture cooled and extracted with ether (2 × 20 c.c.). The aqueous layer was acidified to Congo-red with concentrated hydrochloric acid, and the white precipitate collected and treated with diazomethane in ether. From aqueous methanol the product crystallised as needles, m. p. 73°; mixtures with methyl *cis-trans*- and *cis-cis*-muconate had m. p.s 73—74° and 50—55°, respectively. (iii) Methyl *cis-trans*-muconate (0·5 g.) was heated on the steam-bath with 10% sodium hydroxide solution (1 c.c.) for 30 minutes. The solution was acidified and the white precipitate, m. p. 184°, was treated with diphenyldiazomethane in ether. The product separated from methanol as needles, m. p. 143° undepressed by benzhydryl *cis-trans*-muconate.

Stereochemical Stability of cis-cis-*Muconic Acid and its Esters.*—(i) The acid was stable to boiling methanol and ethanol, as described above. (ii) The finely powdered acid (0·5 g.) was heated at 100° for 4 hours, without protection from light and air, and then treated with diazomethane in ether. A quantitative yield of methyl *cis-cis*-muconate was obtained, m. p. and mixed m. p. 73·5°, depressed to 50—55° by methyl *cis-trans*-muconate. (iii) A solution of the acid (0·5 g.) in aqueous sodium hydroxide (25 c.c.; 0·1N.) was kept at room temperature for 4 days, without protection from light. The solution was then acidified to Congo-red with concentrated hydrochloric acid and cooled to 0° for 4 hours (in the dark), and the precipitate treated with ethereal diazomethane. The product (500 mg., 83%) had m. p. 71—72° undepressed by methyl *cis-cis*-muconate but depressed to 50—55° by the *cis-trans* ester. (iv) A solution of the acid (0·5 g.) in aqueous sodium hydroxide (25 c.c.; 0·1N.) was heated to boiling for 1 minute, cooled, acidified, and kept at 0° as above. Reaction of the precipitate with ethereal diazomethane gave a crystalline solid (0·5 g.), m. p. 70—72° undepressed by methyl *cis-cis*-muconate but depressed to 50—55° by the *cis-trans* ester. (v) The acid (95 mg.) was dissolved in aqueous sodium hydroxide (2 c.c.; 0·4N.) contained in a 1-cm. quartz cell and exposed for 3 minutes to the radiation from a condensed spark between tungsten-steel electrodes (this was thrice the irradiation received during determination of the ultra-violet absorption spectrum). The solution was acidified to Congo-red with concentrated hydrochloric acid and kept at 0° for 4 hours in the dark. The *cis-cis*-muconic acid (80 mg., 85%) thus recovered was converted by diazomethane into the ester (85 mg.), m. p. 70—72°, which did not depress the m. p. of authentic methyl *cis-cis*-muconate but depressed that of the *cis-trans* ester. (vi) A solution of the acid (0·5 g.) in ethanol (10 c.c.) was irradiated for 30 minutes with ultra-violet light from a Hanovia lamp. Evaporation of the solution under reduced pressure and reaction of the residue with diazomethane gave only methyl *cis-cis*-muconate (needles from aqueous methanol), m. p. and mixed m. p. 73·5°. (vii) 50-Mg. samples of the methyl and the benzhydryl ester of *cis-cis*-muconic acid in ethanol were similarly irradiated with ultra-violet light for 15 minutes. The recovered esters had m. p.s 73° and 157°, respectively, undepressed by the corresponding esters of authentic *cis-cis*-muconic acid.

Inversion Experiments.—(a) *Conversion of* cis-cis- *into* cis-trans-*muconic acid.* (i) *cis-cis*-Muconic acid (2 g.) was heated to boiling with just sufficient water to effect solution. When the filtrate was cooled, small prismatic needles of *cis-trans*-muconic acid separated (yield, 95%), m. p. 190—191° •, depressed on admixture with the starting material. The acid was treated with ethereal diazomethane and the product crystallised from methanol–water to give needles of methyl *cis-trans*-muconate, m. p. and mixed m. p. 75°, depressed to 50—55° by the *cis-cis*-ester.

(ii) Crude *cis-cis*-muconic acid (1 g.), direct from the oxidation of phenol (above), was divided into two equal portions, one of which was crystallised from boiling ethanol and the other from boiling water. The recovered acids were each divided into two portions, one of which was treated with diazomethane and the other with diphenyldiazomethane. The four esters thus obtained were recrystallised in the usual way, and mixed m. p. determinations with the appropriate authentic *cis-cis* and *cis-trans* esters made as indicated:



(b) *Conversion of* cis-cis- *and* cis-trans- *into* trans-trans-*muconic acid.* (i) 100-Mg. samples of *cis-cis-* and *cis-trans*-muconic acids were separately dissolved in 5-c.c. portions of methanol containing a trace of iodine and simultaneously irradiated with ultra-violet light from a Hanovia lamp. In each case a precipitate began to form after 2 minutes. After 15 minutes' irradiation, the precipitates were collected: each weighed 95 mg. (95%) and had m. p. 301° undepressed by authentic *trans-trans*-muconic acid. (ii) In a second experiment the two solutions were simultaneously irradiated with light from a 100-watt electric lamp. In each case precipitates began to form after 8 minutes. After a total of 15 minutes, the precipitates were collected and each again was found to weigh 95 mg. and have m. p. 301°. (iii) A solution of *cis-cis*-muconic acid (0·1 g.) in ethanol (10 c.c.) containing a trace of iodine was kept in diffuse daylight for 20 days. *trans-trans*-Muconic acid (0·08 g.) separated as beautiful small laths, m. p. 300—301° undepressed by an authentic specimen.

(c) *Conversion of methyl and benzhydryl* cis-cis-*muconates into the* trans-trans-*muconates.* 50-Mg. samples of the two *cis-cis*-esters were separately dissolved in ethanol containing a trace of iodine and irradiated for 60 minutes with ultra-violet light from a Hanovia lamp. Evaporation of the solutions gave respectively methyl *trans-trans*-muconate, m. p. 154° and mixed m. p. 154—157°, and benzhydryl *trans-trans*-muconate, m. p. 188° and mixed m. p. 188—190°.

(d) *Attempted conversion of* cis-cis- *into* trans-trans-*muconic acid: formation of the butanolidobutanolide* (VII). 3 : 7-*diketo*-2 : 6-*dioxa*bicyclo[3 : 3 : 0]*octane.* (i) *cis-cis*-Muconic acid (0·5 g.) was heated under reflux with water (5 c.c.) for 3 hours. On cooling, crystals of *cis-trans*-muconic acid separated (50 mg.), m. p. 184—188° (moderately rapid rate of heating), identified by reaction with diazomethane to yield methyl *cis-trans*-muconate (needles from methanol–water), m. p. and mixed m. p. 75°. Evaporation of the aqueous filtrate to dryness on the steam-bath afforded a solid which dissolved almost completely in ethanol (5 c.c.). After treatment with charcoal, and filtration, the solution was concentrated to small bulk, and benzene (2 c.c.) added. At 0° colourless plates separated: recrystallised from ethanol–benzene the butanolidobutanolide (Elvidge, Linstead, Orkin, Sims, Baer, and Pattison, *loc. cit.*) formed platelets (0·2 g.), m. p. 131° (Found: C, 50·7; H, 4·3. Calc. for $C_8H_8O_4$: C, 50·7; H, 4·25%). The compound depressed the m. p. of γ-carboxymethyl-Δ^{α}-butenolide and was insoluble in aqueous sodium hydrogen carbonate. When kept for several days with water, the solution became acidic. (ii) *cis-cis*-Muconic acid (0·5 g.) was heated under reflux with water (5 c.c.) containing a few drops of concentrated hydrochloric acid, and after 30 minutes the mixture was evaporated to dryness on the water-bath. The residual oil crystallised on cooling; from ethanol–benzene the product separated as plates (0·3 g., 60%), m. p. 129—130° undepressed by the previously obtained dilactone.

Conversion of γ-Carboxymethyl-Δ^{α}*-butenolide* (II) *into the Butanolidobutanolide* (VII).—A solution of the lactonic acid (0·5 g.) in water (5 c.c.) containing a few drops of concentrated hydrochloric acid was refluxed for 10 minutes, then evaporated to dryness on the water-bath to give an oil which set to a solid on cooling. From ethanol–benzene the butanolidobutanolide (0·3 g.) formed small plates, m. p. and mixed m. p. 128—129°. A mixture with the lactonic acid had m. p. 91—98°.

We are indebted to Mr. J. L. Hales of the Chemical Research Laboratory for the infra-red spectral data, and to Dr. E. A. Braude for the ultra-violet absorption determinations. One of us (P. S.) gratefully acknowledges a grant from the Ministry of Education.

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463. *Organic Fluoro-compounds. Part II. The Preparation of Alkyl 2 : 4-Dinitrophenyl Ethers from 1-Fluoro-2 : 4-dinitrobenzene.*

By W. B. Whalley.

The interaction of 1-fluoro-2 : 4-dinitrobenzene with alcohols in the presence of triethylamine readily furnishes the corresponding 2 : 4-dinitrophenyl ethers, which are suitable in many instances for the characterisation of the alcohols.

The 2 : 4-dinitrophenyl ethers of phenols are readily preparable by the interaction of an alcoholic solution of 1-chloro-2 : 4-dinitrobenzene and a solution of the phenol in aqueous sodium hydroxide (Bost and Nicholson, *J. Amer. Chem. Soc.*, 1935, **57**, 2368). In general 1-chloro-2 : 4-dinitrobenzene does not react readily wth alcohols and those 2 : 4-dinitrophenyl ethers of alcohols reported have usually been formed by the interaction at an elevated temperature, of the appropriate sodium alkoxide and the reagent (*e.g.*, Blanksma and Van der Weyden, *Rec. Trav. chim.*, 1940, **39**, 629), or by indirect methods such as ether exchange (Ogata and Okano, *J. Amer. Chem. Soc.*, 1949, **71**, 3211, 3212).

The easy replacement of a fluorine atom, located in the *ortho-* or *para*-position to a nitro-group, by an alkoxyl group under the influence of methyl or ethyl alcoholic potassium hydroxide (Schiemann, *Ber.*, 1929, **62**, 1794; Brown, Suckling, and Whalley, *J.*, 1949, S95) suggested the use of 1-fluoro-2 : 4-dinitrobenzene for the general production of the 2 : 4-dinitrophenyl ethers of alcohols. The present communication records that alcohols and 1-fluoro-2 : 4-dinitro-

2 : 4-*Dinitrophenyl ethers.*

Alcohol.	M. p.	Crystalline form.	Formula.	Found, %. C.	H.	N.	Required, %. C.	H.	N.
Methyl alcohol	87° [a]	Glistening plates [1]	$C_7H_6O_5N_2$	42·6	3·2	14·3	42·4	3·0	14·2
*iso*Propyl alcohol	56 [a]	Needles [1]	$C_9H_{10}O_5N_2$	47·8	4·5	12·2	47·8	4·4	12·4
*iso*Butyl alcohol	35 [b]	Plates [1]	$C_{10}H_{12}O_5N_2$	50·1	5·1	11·9	50·0	5·0	11·7
Allyl alcohol	45 [b]	Very pale yellow needles [1]	$C_9H_8O_5N_2$	48·5	3·5	13·2	48·2	3·6	12·5
2-Phenylethyl alcohol	88	Massive long slender prisms [1]	$C_{14}H_{12}O_5N_2$	58·3	4·3	9·8	58·3	4·2	9·7
Cinnamyl alcohol	135	Pale greenish-yellow long slender needles [1]	$C_{15}H_{12}O_5N_2$	60·2	4·2	9·9	60·0	4·0	9·3
Benzyl alcohol	150 [c]	Plates [b]	$C_{13}H_{10}O_5N_2$	57·1	3·5	10·3	56·9	3·7	10·2
m-Nitrobenzyl alcohol	168	Slender prisms [a]	$C_{13}H_9O_7N_3$	48·7	3·0	13·4	48·9	2·8	13·2
p-Nitrobenzyl alcohol	207 [a]	Shimmering flat prisms [b]	$C_{13}H_9O_7N_3$	48·9	2·9	13·1	48·9	2·8	13·2
(−)-3-(6 : 6-Dimethoxy-*o*-tolyl)butan-2-ol	124	Pale lemon-yellow glistening plates [1]	$C_{19}H_{22}O_7N_2$	58·6	5·7	7·2	58·5	5·6	7·2
Benzoin	226	Slender flat prisms [b]	$C_{20}H_{14}O_8N_4$	63·3	3·9	7·6	63·5	3·7	7·4
Ethylene glycol	212	Pale yellow plates [b]	$C_{14}H_{10}O_{10}N_4$	42·7	2·7	14·3	42·6	2·5	14·2
Ethylene glycol monomethyl ether	38	Needles [1]	$C_9H_{10}O_6N_2$	44·8	4·2	11·9	44·6	4·1	11·6
Propylene glycol	157	Clusters of very small needles [b]	$C_{15}H_{14}O_{10}N_4$	44·4	3·2	13·9	44·1	2·9	13·7
Trimethylene glycol	187	Glistening prisms [b]	$C_{15}H_{14}O_{10}N_4$	44·3	3·0	14·0	44·1	2·9	13·7
Cetyl alcohol	60	Feathery needles [1]	$C_{28}H_{44}O_5N_2$	64·7	9·2	6·6	64·7	8·5	6·9
Borneol	128	Needles [1]	$C_{16}H_{20}O_5N_2$	60·2	6·3	9·1	60·0	6·3	8·8
Ergosterol	180	Long slender glistening very pale yellow needles [b]	$C_{34}H_{44}N_2O_5$	72·7	8·3	5·0	72·6	8·2	5·0

[1] Crystallised from methyl alcohol or aqueous methyl alcohol. [a] Crystallised from acetic acid. [b] Ogata and Okano (*loc. cit.*) give m. p. 34—35°. [c] Blanksma and Van der Weyden (*loc. cit.*) record m. p. 46°. Ogata and Okano (*loc. cit.*) give m. p. 51—53°. [d] Fairbourne and Toms (*J.*, 1921, **119**, 1035) record m. p. 46° for a specimen prepared in low yield by the refluxing of a mixture of allyl alcohol and 1-chloro-2 : 4-dinitrobenzene. [e] Staedel (*Annalen*, 1883, **217**, 177) and Holmes and Ingold (*J.*, 1925, **127**, 1810) describe the product as orange-yellow needles, m. p. 198°. Lyman and Reid (*J. Amer. Chem. Soc.*, 1920, **42**, 616) record m. p. 248° for a substance which was apparently not analysed. [f] Kumpf (*Annalen*, 1884, **224**, 128) records m. p. 149° for a substance prepared by the interaction of benzyl iodide and the silver salt of 2 : 4-dinitrophenol. Raiford and Colbert (*J. Amer. Chem. Soc.*, 1926, **48**, 2659) give m. p. 149·5°. [g] Post and Mehrtens (*Ber.*, 1875, **8**, 1552) record m. p. 87°.

benzene react easily in the presence of triethylamine, as a catalyst, with the production, usually in high yield, of the corresponding ethers which in many cases are highly crystalline solids suitable for the characterisation of the alcohols [cf. the use of 1-fluoro-2 : 4-dinitrobenzene for the characterisation of amino-acids (Sanger, *Biochem. J.*, 1945, **39**, 507)].

Pyridine is not a suitable catalyst; interaction with the reagent produces dark resinous products.

Primary alcohols react very readily and exothermically, whilst secondary and tertiary alcohols react less readily and frequently require warming to complete the reaction. Unsaturated alcohols (*e.g.* allyl alcohol, cinnamyl alcohol, cholesterol, and ergosterol; see table) appear to react normally: the two ketonic alcohols examined (benzoin and diacetone alcohol) appeared to suffer considerable decomposition.

As a reagent for the characterisation of alcohols, 1-fluoro-2 : 4-dinitrobenzene would appear to offer considerable advantages over the conventional reagents which require careful storage under anhydrous conditions and in general necessitate the use of the anhydrous alcohol. In contrast, 1-fluoro-2 : 4-dinitrobenzene is quite stable to atmospheric moisture and may apparently be stored indefinitely without the observance of special precautions designed to prevent the ingress of water. Small amounts of water do not appear seriously to impair the yield of derivative, and any 2 : 4-dinitrophenol produced by the hydrolysis of the reagent is readily removable (contrast, for example, the behaviour of the *iso*cyanates, "Organic Reagents for Organic Analysis," 1944, London, p. 11).

Experimental.

1-Fluoro-2 : 4-dinitrobenzene.—*p*-Fluoronitrobenzene (Balz and Schiemann, *Ber.*, 1927, **60**, 1186) was nitrated by Holleman and Beekmann's method (*Rec. Trav. chim.*, 1904, **23**, 253).

Alkyl 2 : 4-Dinitrophenyl Ethers.—The general method of preparation consists of the interaction of equimolecular quantities of the reagents in the presence of a little triethylamine. Reaction may occur at room temperature, rapidly or during several hours, or when the mixture is heated on the steam-bath

for several hours. No solvent is necessary for liquid alcohols, but solids require the use of a solvent; benzene or ether is convenient, benzene being preferable where heating is required to complete the reaction. The product frequently crystallises from the dark reaction mixture which is decomposed by the addition of excess of dilute hydrochloric acid; the crude 2 : 4-dinitrophenyl ether is collected by filtration (if a solid) or ether extraction (if an oil) and freed from any 2 : 4-dinitrophenol by washing it with aqueous sodium hydrogen carbonate. The product may be crystallised from alcohol, aqueous alcohol, or frequently more conveniently from glacial acetic acid as many of the ethers are only sparingly soluble in alcohols and prolonged heating to ensure solution is undesirable because of the dangers of trans-etherification. One crystallisation is usually sufficient to remove the small quantities of dark by-products.

The following typical preparations illustrate variations of the general method:

(a) 2 : 4-*Dinitrophenetole.*—Triethylamine (3 drops) was added to a solution of 1-fluoro-2 : 4-dinitrobenzene (0·5 g.) in excess of 95% ethyl alcohol. The solution darkened, heat was evolved, and the product separated on cooling. 30 Minutes later excess of N-hydrochloric acid solution was added and the solid was collected, washed with 2N-sodium hydrogen carbonate solution, and crystallised from aqueous ethyl alcohol whereupon 2 : 4-dinitrophenetole (0·5 g.) separated in almost colourless glistening plates, m. p. 85° (Found: C, 45·4; H, 3·9; N, 13·5. Calc. for $C_8H_8O_5N_2$: C, 45·3; H, 3·8; N, 13·2%). Blanksma and Van der Weyden (*loc. cit.*) give m. p. 85°.

(b) 2 : 4-*Dinitrophenyl n-propyl ether.* To a solution of 1-fluoro-2 : 4-dinitrobenzene (0·5 g.) in *n*-propyl alcohol (0·2 g.), triethylamine (3 drops) was added. 12 Hours later the dark mixture was acidified by the addition of excess of N-hydrochloric acid, the precipitated oil extracted with ether (3 × 20 ml.), the extract washed with 2N-aqueous sodium hydrogen carbonate, dried, and evaporated, and the residue crystallised from aqueous methyl alcohol whereupon 2 : 4-dinitrophenyl *n*-propyl ether (0·4 g.) separated in almost colourless needles, m. p. 29° (Found: C, 47·8; H, 4·5; N, 12·7. Calc. for $C_9H_{10}O_5N_2$: C, 47·8; H, 4·4; N, 12·4%). Blanksma and Van der Weyden (*loc. cit.*) record m. p. 32°; Ogata and Okano (*loc. cit.*) record m. p. 28—30°.

(c) *Cholesteryl* 2 : 4-*dinitrophenyl ether.* A solution of cholesterol (0·3 g.), 1-fluoro-2 : 4-dinitrobenzene (0·2 g.), and triethylamine (0·5 ml.) in benzene (5 ml.) was heated on the steam-bath for 4 hours. The product partly crystallised from the cooled solution, which was decomposed with excess of N-hydrochloric acid solution and extracted with ether (3 × 20 ml.), and the extract washed with 2N-aqueous sodium hydrogen carbonate until the washings were colourless, dried, and evaporated. *Cholesteryl* 2 : 4-*dinitrophenyl ether* (0·3 g.) separated from acetic acid in very pale greenish-yellow, long, slender needles, m. p. 172° (Found: C, 71·9; H, 8·9; N, 5·0. $C_{33}H_{48}O_5N_2$ requires C, 71·7; H, 8·7; N, 5·1%).

tert.-Butyl alcohol and *n*-octyl alcohol furnished 2 : 4-dinitrophenyl ethers which crystallised at 0° but were oils at room temperature. *tert.*-Amyl alcohol, *n*-butyl alcohol, ethylene glycol monoethyl ether, and *cyclo*hexanol gave derivatives which could not be crystallised at 0°. Diacetone alcohol gave a low-melting crystalline solid accompanied by much dark oil.

Caution: 1-Fluoro-2 : 4-dinitrobenzene is a skin irritant and should be handled accordingly.

The author thanks Mr. N. Lund, B.Sc., for assistance with the preparation of *p*-fluoronitrobenzene, and Imperial Chemical Industries Limited (General Chemicals Division) for a gift of sodium fluoroborate.

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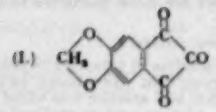
NOTES.

Studies on Indene Derivatives. Part VIII. *Methylenedioxyindanetrione.* By RADWAN MOUBASHER.

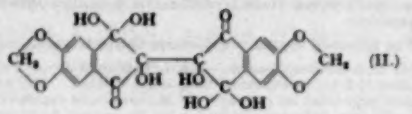
5 : 6-METHYLENEDIOXYINDANE-1 : 2 : 3-TRIONE (I) is obtained when the corresponding hydrate is heated in a vacuum at 250° or treated with thionyl chloride or oxalyl chloride (cf. Ruhemann, *J.*, 1912, **101**, 780). When suspended in *iso*propyl alcohol and exposed to sunlight, or treated with the Gomberg–Bachmann reagent (*J. Amer. Chem. Soc.*, 1927, **49**, 236), (I) was reduced to the colourless hydrindantin (II). Prolonged treatment of (I) with hydrogen sulphide gave the substance (III; R = H). Since (II) behaved similarly it probably represents an intermediate stage in the reduction. Substance (III) gave the dimethyl ether (III; R = Me) on treatment with diazomethane. With α-amino-acids, the hydrate of (I) gave a mixture of (II) and (III; R = H) (cf. Moubasher and Ibrahim, *J.*, 1949, 702), and with dilute ammonia the benzoylglyoxalinoindenone (IV). As shown by Ruhemann (*loc. cit.*), heating (IV) alone or in acetic acid or acetic anhydride gave a red compound formulated as (V) or (VI) (cf. Moubasher, *J.*, 1949, 1038).

Photo-chemical Reaction between 5 : 6-*Methylenedioxyindane*-1 : 2 : 3-*trione and* iso*Propyl Alcohol.*—Freshly prepared triketone (0·5 g.) suspended in freshly distilled *iso*propyl alcohol (10 g.; dried with calcium carbide) in a closed Monax tube filled with carbon dioxide was exposed to sunlight for 15 days (March). The red substance gradually disappeared and a colourless solid was formed. The excess of *iso*propyl alcohol was removed in a vacuum, and the residue (0·3 g.) crystallised from aqueous acetone. The photo-product showed the properties of *di*-(5 : 6-*methylenedioxy*)*hydrindantin* (II); it turned red at about 120° and decomposed at 278° with evolution of gas; it formed an intense blue solution in sodium hydroxide solution. It crystallises from acetone–alcohol (Found: C, 53·5; H, 3·0. $C_{33}H_{14}O_{13}$ requires C, 53·8; H, 3·1%).

Action of Gomberg–Bachmann's Reagent.—To powdered magnesium (4 g.) in a mixture of dry ether (50 c.c.) and dry benzene (50 c.c.; thiophen-free) iodine was added until its colour persisted. Dry magnesium powder (4 g.) was then added, followed by the anhydrous triketone (I) (0·3 g.), and the mixture was shaken at room temperature for ½ hour and then refluxed for another ½ hour. The product was added to ice-cold dilute hydrochloric acid and left overnight in an open vessel. The deposit was then filtered off and crystallised from acetone–alcohol, the hydrindantin (II) (0·2 g.) being obtained as colourless crystals (identified by m. p., mixed m. p., and properties).



(I.)



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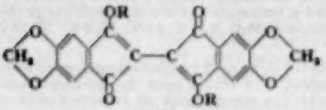

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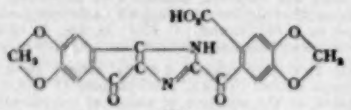
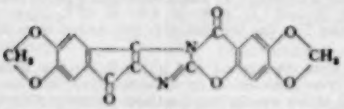
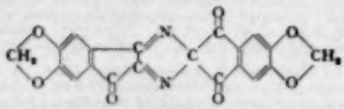


(IV.)



(V.)



(VI.)

Action of Oxalyl Chloride on Di-(5 : 6-methylenedioxy)hydrindantin Hydrate.—0·2 G. of (II) was refluxed with 10 c.c. of oxalyl chloride for ½ hour, and the excess of oxalyl chloride removed by distilling under a vacuum; the colourless residue recrystallised from much dry benzene in colourless needles of di-(2-dihydroxy-1 : 3-diketo-5 : 6-methylenedioxyindan-2-yl), m. p. 288° (Found: C, 58·1; H, 2·6. Calc. for $C_{20}H_{14}O_{10}$: C, 58·5; H, 2·4%).

Formation of Di-(2-hydroxy-3-keto-5 : 6-methylenedioxyinden-2-yl) (III; R = H).—(a) *From the hydrate of* (I). The triketone hydrate (0·2 g.) in ethyl alcohol (90%; 150 c.c.) was refluxed for 3 hours, during which a stream of hydrogen sulphide was passed through the mixture; after some hours at room temperature the crystals were filtered off and recrystallised from 2-methylnaphthalene in dark violet crystals, m. p. 340° (*ca.* 50%), soluble in aqueous sodium hydroxide to a dark red solution (Found: C, 65·2; H, 2·5. Calc. for $C_{20}H_{12}O_8$: C, 63·4; H, 2·7%).

(b) *From the hydrindantin.* The procedure was as described under (a), the yield being *ca.* 70%.

The powdered substance reacted vigorously with ethereal diazomethane, dissolving in the cold after 24 hours; after evaporation, the residue of the dimethyl ether crystallised from methyl alcohol in orange crystals, m. p. 170° (decomp.), soluble in alcohol, difficulty soluble in ether, and insoluble in sodium hydroxide solution (Found: C, 64·8; H, 3·2. Calc. for $C_{22}H_{16}O_8$: C, 65·0; H, 3·4%).

The dimethyl ether was treated with cold sulphuric acid for 2 hours at 60°. The red-violet solution was poured into ice-cold water, giving a red-violet deposit of (III; R = H) which, dried and crystallised, had m. p. 340° undepressed by an authentic sample prepared as above.

Action of Oxygen on (III; R = H) *in Presence of Selenium.*—The substance (0·2 g.) was powdered with red selenium (2 g.) and heated at 320° in a current of air for 3 hours. A sublimate of colourless crystals, after recrystallisation from hot water, was identified as hydrastic acid.

Action of 5 : 6-Methylenedioxyindane-1 : 2 : 3-trione Hydrate on α-Amino-acids.—(a) A solution of 0·2 g. of alanine in 25 c.c. of water was added to a suspension of 0·3 g. of the hydrate in 100 c.c. of water in a Claisen flask fitted with an upright condenser, to which was attached a sloping condenser and a receiver, whilst a continuous current of carbon dioxide was passed through the whole. The receiver contained a solution of 2 : 4-dinitrophenylhydrazine hydrochloride. The mixture in the flask was distilled until its volume was reduced to about 25 c.c. The receiver was then left to cool, whereupon acetaldehyde 2 : 4-dinitrophenylhydrazone (*ca.* 30%) was obtained, having m. p. 166° (cf. Bryant, *J. Amer. Soc.*, 1932, **54**, 3760) alone or mixed with an authentic sample.

In the reaction vessel a dark red-violet substance separated, which was filtered off, dried, and recrystallised from 2-methylnaphthalene giving (III; R = H) in needles (0·1 g.).

(*b*) Heating a mixture of alanine (0·2 g.) with the hydrate (0·3 g.) in 50 c.c. of water gave carbon dioxide and ammonia.

Action of Aqueous Ammonia on the Indanetrione Hydrate.—The hydrate (0·2 g.), dissolved in hot water (100 c.c.), was cooled and excess of aqueous ammonia was added, a violet solution being obtained. After ½ hour at room temperature this was filtered and acidified with concentrated hydrochloric acid. The resulting brownish-red gelatinous precipitate of 5 : 6-*methylenedioxy*-2′-(2-*carboxy*-4 : 5-*methylene*-

dioxylbenzoyl)glyoxalino(4′ : 5′-2 : 3)*indan*-1-*one* (IV) was filtered off, washed with hot water, dried, and crystallised from dioxan–ethyl alcohol, forming scarlet prisms (0·1 g.), which changed at 350° to an intensely red solid and melted at 380° (decomp.) (varies with the rate of heating). The substance is soluble in aqueous ammonia and alkali and is reprecipitated by acids (Found: C, 58·6; H, 2·2; N, 6·6. $C_{20}H_{12}O_4N_2$ requires C, 59·1; H, 2·4; N, 6·8%).

The powdered product (0·1 g.) with an excess of ethereal diazomethane gave a *methyl* ester, red needles (from methyl alcohol) (0·09 g.), m. p. 320 (red melt), insoluble in aqueous alkali and alkali carbonate (Found: C, 60·4; H, 2·8; N, 6·8. $C_{21}H_{14}O_4N_2$ requires C, 60·0; H, 2·8; N, 6·6%).

When boiled in acetic anhydride (25 c.c.) or acetic acid (50 c.c.) for ½ hour and then cooled, (IV) gave the *anhydro*-compound (V or VI) as a crystalline red deposit, which was filtered off and recrystallised from glacial acetic acid in intensely red prisms (0·09 g.), m. p. 380°, insoluble in cold or hot ammonia solution (Found: C, 61·7; H, 1·8; N, 6·8. $C_{20}H_{10}O_3N_2$ requires C, 61·8; H, 2·0; N, 7·1%). The same substance was obtained when (IV) was heated in a vacuum at 360°/4 mm.—FOUAD I UNIVERSITY, FACULTY OF SCIENCE, CAIRO, EGYPT. [*Received, April 11th*, 1950.]

The Action of Ammonia on β-Benzoylacrylic Acid. By M. M. FRASER and R. A. RAPHAEL.

THE action of ammonia on β-benzoylacrylic acid has been studied by Bougault (Bougault, *Ann. Chim.*, 1908, **15**, 491; Bougault and Chabrier, *Compt. rend.*, 1948, **226**, 1378). At first the product was tentatively described as α-amino-β-benzoylpropionic acid but in the later communication this was altered to β-amino-β-benzoylpropionic acid; in neither case were the formulations accompanied by analyses or chemical evidence of structure. The mode of addition giving rise to the β-amino-acid would be surprising (cf. Jones, Shen, and Whiting, *J.*, 1950, 236) especially as an α-amino-ketone such as this would be expected to undergo ready self-condensation to a dihydropyrazine. Because of the potentialities of this approach to the synthesis of kynurenin (α-amino-β-2-aminobenzoylpropionic acid) an investigation of this reaction has been undertaken and chemical evidence has been adduced which shows the product to be the α-amino-acid.

In the ninhydrin reaction the product does not give results typical of an α-amino-acid; during prolonged boiling an orange coloration slowly develops, followed by the sudden formation of a white crystalline precipitate possessing properties identical with Ruhemann's hydrindantin (Ruhemann, *J.*, 1911, **99**, 792, 1306; cf. West and Rinehart, *J. Biol. Chem.*, 1942, **146**, 105). In any event this colour reaction would not serve as a discriminatory test between the two structures since α-amino-ketones also give colorations under such conditions (Cherbuliez and Herzenstein, *Helv. Chim. Acta*, 1934, **17**, 1440). Reduction of the keto-amino-acid with sodium amalgam furnished the corresponding hydroxy-amino-acid which gave an intense purple coloration on being gently warmed with aqueous ninhydrin solution. The original product is therefore correctly formulated as the α-amino-acid. This conclusion was confirmed by the nitrous acid deamination of the original product whereupon the well-characterised α-hydroxy-β-benzoylpropionic acid was obtained, the structure of which has been established by its preparation by the hydrolysis of chloral-acetophenone (Konigs, *Ber.*, 1882, **15**, 557).

The atypical ninhydrin reaction given by α-amino-β-benzoylpropionic acid is probably due to the immediate interaction of the two degradation products, ammonia and hydroxymethyleneacetophenone, to form the stable aminomethylene compound; the non-availability of the ammonia would preclude the formation of the characteristic deep-blue coloration.

Experimental.—β-Benzoylacrylic acid (5 g.) was dissolved in ammonia (30 c.c.; *d* 0·88). After 16 hours the liquid was concentrated *in vacuo* to about 5 c.c.; the precipitated white solid (4·1 g.) consisting of the keto-amino-acid was filtered off and washed with water. The crude product was dissolved in warm 6*N*-hydrochloric acid; on cooling the *hydrochloride* crystallised rapidly in plates, m. p. 202° (Found: C, 52·5; H, 5·5; N, 5·9. $C_{10}H_{11}O_3N,HCl$ requires C, 52·4; H, 5·3; N, 6·1%). Treatment of an aqueous solution of the hydrochloride with the requisite quantity of dilute ammonia solution resulted in the crystallisation of the free *keto-amino-acid*, which crystallised from aqueous alcohol in plates, m. p. 197° (decomp.; rapid heating) (Found: C, 62·25; H, 5·75; N, 7·15. $C_{10}H_{11}O_3N$ requires C, 62·15; H, 5·75; N, 7·2%).

The presence of the carbonyl, amino-, and carboxyl groups was confirmed by preparation of the relevant derivatives: the *benzoyl* derivative, made by the usual Schotten–Baumann procedure, crystallised from alcohol in needles, m. p. 182° (Found: C, 66·8; H, 5·3; N, 4·9. $C_{17}H_{15}O_4N$ requires C, 66·85; H, 5·1; N, 4·7%); the action of diazomethane in acetone solution on this derivative furnished the corresponding *methyl* ester, m. p. 116°, crystallising from alcohol in needles (Found: C, 69·9; H, 5·5; N, 4·6. $C_{18}H_{17}O_4N$ requires C, 69·5; H, 5·5; N, 4·5%). The action of semicarbazide acetate on the benzoyl derivative yielded the corresponding *semicarbazone*, crystallising from alcohol in needles, m. p. 187° (Found: C, 61·3; H, 5·0; N, 15·6. $C_{18}H_{18}O_4N_4$ requires C, 61·0; H, 5·1; N, 15·8%). Treatment of the benzoyl derivative with ethanolic 2 : 4-dinitrophenylhydrazine sulphate furnished the corresponding 2 : 4-*dinitrophenylhydrazone ethyl* ester, m. p. 196°, crystallising from alcohol in orange rosettes (Found: C, 59·6; H, 4·7; N, 13·8. $C_{25}H_{22}O_7N_4$ requires C, 59·4; H, 4·6; N, 13·85%).

Reduction. The keto-amino-acid (3 g.) was dissolved in the minimum amount of warm aqueous acetic acid (*ca.* 30 c.c.; 20%) and alcohol (70 c.c.) added. Sodium amalgam (from 48 g. of mercury and 2·4 g. of sodium) was added slowly with stirring during two hours; after a further 30 minutes the solution was filtered to remove unchanged material (0·8 g.). The filtrate was concentrated *in vacuo* to 15 c.c.; on cooling the hydroxy-amino-acid (1·5 g.) crystallised. Crystallisation from water gave prisms, m. p. 219° (decomp.; rapid heating) (Bougault and Chabrier, *loc. cit.*, give m. p. 215°) (Found: C, 61·35; H, 6·25; N, 7·2. $C_{10}H_{11}O_3N$ requires C, 61·5; H, 6·7; N, 7·15%). This hydroxy-amino-

acid gave a strongly positive ninhydrin reaction. Although in theory the reduction should produce two racemates in practice only the one product was isolated.

An attempted reduction to α-amino-γ-phenylbutyric acid by a modified Kishner–Wolff procedure (Huang-Minlon, *J. Amer. Chem. Soc.*, 1946, **68**, 2487) resulted in the production of γ-phenylbutyric acid.

Deamination. The keto-amino-acid hydrochloride (2 g.) was dissolved in water (10 c.c.), and an aqueous solution of sodium nitrite (1 g.) added slowly in the cold. The solution was filtered from a small amount of gummy material, and the filtrate acidified with dilute sulphuric acid. The resulting turbid solution was kept at 0° for 16 hours. The solid thus formed was filtered off, dried, and crystallised from carbon tetrachloride, from which solvent it formed small prisms, m. p. 125—125·5° undepressed on admixture with an authentic specimen of α-hydroxy-β-benzoylpropionic acid (Rice, *J. Amer. Chem. Soc.*, 1923, **45**, 229, gives m. p. 126°).

If the deamination was carried out in hydrochloric acid solution the product was found to be α-chloro-β-benzoylpropionic acid, m. p. 113° (decomp.) undepressed on admixture with an authentic sample (Bougault, *loc. cit.*, gives m. p. 114°) (Found: C, 56·65; H, 4·35. Calc. for $C_{10}H_9O_3Cl$: C, 56·5; H, 4·25%). This radical interchange during such deamination reactions has been noted before (Jochem, *Z. physiol. Chem.*, 1900, **31**, 119).

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The Oxidation of Anthrone by Aromatic Nitro-compounds. By V. M. Ingram.

Attempts to prepare 10-*m*-nitrodiphenylmethyleneanthrone by the condensation of anthrone with dichloro-*m*-nitrodiphenylmethane in boiling xylene were unsuccessful (cf. Schönberg *et al.*, *J.*, 1946, 442); the nitro-compound acted as an oxidising agent converting the anthrone into dianthron-9-yl.* The same oxidising action was also shown by nitrobenzene, *m*-nitrobenzaldehyde, and *m*-nitrobenzophenone, and it would thus appear to be a general characteristic of aromatic nitro-compounds.

With nitrobenzene, which underwent reduction to aniline, it was found that the yield of dianthron-9-yl was greatly improved by carrying out the oxidation in the presence of hydrogen chloride, but was very seriously diminished when a little piperidine was added to the reaction mixture.

Experimental.—(M. p.s are uncorrected.) *Oxidation of anthrone.* (a) *By dichloro-m-nitrodiphenylmethane.* The keto-chloride was prepared by heating molecular proportions of *m*-nitrobenzophenone and phosphorus pentachloride on the water-bath for 8 hours. After being cooled, filtered from unchanged ketone, and freed from phosphorus oxychloride by distillation with petroleum (b. p. 100—120°) under diminished pressure, the crude keto-chloride solidified overnight and was used without further purification.

A solution of anthrone (20 g.) and this chloride (35 g.) in xylene (100 c.c.) was boiled for 2 hours. When cooled the solution deposited dianthron-9-yl (12·5 g., 63%) which, after crystallisation from acetic acid–methyl salicylate (2 : 1), had m. p. 266—267° (decomp.) not depressed by admixture with an authentic specimen prepared according to Barnett (*J.*, 1923, 387).

(b) *By nitrobenzene.* A solution of anthrone (5·0 g.) and nitrobenzene (3·0 c.c.) in dry xylene (30 c.c.), containing a little hydrogen chloride, was boiled under reflux for 5 hours. Leaflets of aniline hydrochloride and drops of water appeared in the condenser, and, when cooled, the liquid, which had become dark orange, furnished dianthron-9-yl (4·2 g., 86%) in an almost pure condition.

The xylene mother-liquor was extracted several times with small portions of dilute hydrochloric acid. On the addition of bromine (in acetic acid) to the acid extract *s*-tribromoaniline was precipitated and corresponded in amount (0·9 g.) to 82% of that required for the formation of the dianthronyl.

In a further experiment in which the same amounts of nitrobenzene and anthrone were employed, but in which the hydrogen chloride was omitted, the yield of dianthron-9-yl fell to 40%, and when the hydrogen chloride was replaced by piperidine (3 drops) the yield was only 6%.

(c) *By m-nitrobenzophenone.* After being boiled for 5 hours, a solution of anthrone (2·5 g.) and *m*-nitrobenzophenone (3·0 g.) in dry xylene (15 c.c.) deposited unchanged anthrone. Hydrogen chloride was then passed into the liquid and heating continued for a further 2 hours. Extraction of the resulting crystals with a little boiling acetone followed by crystallisation from glacial acetic acid–methyl salicylate (1 : 1) furnished a small amount (0·25 g., 10%) of dianthron-9-yl.

(d) *By m-nitrobenzaldehyde.* A solution of *m*-nitrobenzaldehyde (2·0 g.) and anthrone (2·5 g.) in dry xylene (15 c.c.), after 5 hours' refluxing yielded dianthron-9-yl (0·9 g., 36%).

The oxidation of anthrone to dianthron-9-yl by aromatic nitro-compounds apparently depends on the preliminary treatment of the xylene. In the experiments described above the xylene had been purified by prolonged storage over sodium at ordinary temperature, but other samples which had been more rapidly purified by boiling over sodium, sometimes after previous refluxing with anhydrous aluminium chloride, yielded tarry products from which little or no dianthron-9-yl could be isolated. —Birkbeck College, London, E.C.4. [*Received, April 11th*, 1950.]

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* See footnote, p. 2211.

Preparation of m-Dimethylaminobenzaldehyde. By V. M. Ingram.

m-Dimethylaminobenzaldehyde, which has been previously prepared by Cocker *et al.* (*J.*, 1938, 751) from *m*-nitrobenzaldehyde by a laborious method involving successive conversion into the acetal, reduction, and hydrolysis, followed by the methylation of the resulting *m*-aminobenzaldehyde, can be readily obtained in one operation by the catalytic reduction of *m*-nitrobenzaldehyde in the presence of formaldehyde in alcoholic solution.

Experimental.—(M. p.s and b. p.s are uncorrected.) The catalyst was prepared by stirring a suspension of charcoal (5·0 g.) in an aqueous solution (100 c.c.), containing palladous chloride (1·0 g. dissolved in 1 c.c. of 10*N*-hydrochloric acid) and hydrated sodium acetate (5·0 g.), in an atmosphere of hydrogen at room temperature and pressure until the absorption of hydrogen ceased. After being filtered off and washed with water, the catalyst was added to a solution of *m*-nitrobenzaldehyde (10·0 g., 0·1 mol.) in alcohol (400 c.c.) containing aqueous formaldehyde (60 c.c.; 40%), and the mixture stirred vigorously in hydrogen at ordinary temperature and pressure. The reduction proceeded rapidly at first, but the rate of absorption slowly decreased until after 5 hours it had fallen to zero; the total volume of hydrogen absorbed amounted to 11 l. (theory, 11·2 l. at N.T.P.).

The solution was filtered from the catalyst and acidified with dilute hydrochloric acid, and most of the alcohol was then removed by distillation. After extraction with ether to remove unchanged nitro-compound, the almost black solution was made alkaline with sodium hydroxide, and the amino-aldehyde collected in benzene. On fractionation of the product under reduced pressure *m*-dimethylaminobenzaldehyde was obtained as a pale oil (4·0 g., 27%), b. p. 112—114°/3 mm., and was identified by conversion into *α*-*m*-dimethylaminobenzylideneacetophenone, which had m. p. 105—106°, identical with the value given by Cocker *et al.* (*loc. cit.*).—Birkbeck College, London, E.C.4. [*Received, April 11th*, 1950.]

The Reaction of Diacetyl with Ethyl Orthoformate. By D. A. Harris.

Parfent'ev and Mirzaev (*J. Gen. Chem. Russia*, 1941, **11**, 707) reported that diacetyl reacted with two molecular equivalents of ethyl orthoformate in the presence of a trace of sulphuric acid to give 2 : 2 : 3 : 3-tetraethoxybutane in 69% yield. This reaction has been repeated but the tetraethoxybutane was not obtained. The product, after careful fractionation, showed an absorption band in the ultra-violet ($\varepsilon_{max.}$ 33·8 at $\lambda_{max.}$ 294 mμ.) characteristic in position and intensity for a ketone; and its molecular weight corresponded to that required for 3 : 3-diethoxybutan-2-one. This conclusion was confirmed by a comparison of the physical constants with those reported by Calder and Fleer (U.S.P. 2,401,236; *Chem. Abs.*, 1946, **40**, 5070).

This butanone was prepared more conveniently by reaction of equimolecular proportions of diacetyl and ethyl orthoformate, since the use of two molecular equivalents of the latter gave a product from which the excess of ethyl orthoformate was difficult to fractionate. Another compound with a boiling point between that of ethyl orthoformate and the ketone was formed in a small amount; its presence was detected from its absorption in the ultra-violet at 250 mμ., but it was not identified.

3 : 3-Diethoxybutan-2-one gave the dioxime and disemicarbazone of diacetyl when it reacted with hydroxylamine and semicarbazide, respectively.

Experimental.—Reaction of diacetyl with two molecular equivalents of ethyl orthoformate. Following the directions of Parfent'ev and Mirzaev (*loc. cit.*) diacetyl (14·4 g., 0·167 mol.) was added dropwise to ethyl orthoformate (50·0 g., 0·34 mol.) and sulphuric acid (4 drops). Stirring was continued for four hours at a temperature of 40—50°; the mixture was then taken up in ether, shaken with 10% sodium carbonate solution, washed with water, and dried (K_2CO_3). The ether was removed by distillation and the residue fractionally distilled giving a main fraction (36·8 g.), b. p. 55—65°/20 mm. Re-fractionation yielded 3 : 3-diethoxybutan-2-one (9·5 g., 36%), b. p. 64—65·5°/19 mm [Found: C, 59·8; H, 10·1%; *M* (cryoscopic in benzene), 167. Calc. for $C_8H_{16}O_3$: C, 60·0; H, 10·0%; *M*, 160].

Reaction of diacetyl with one molecular equivalent of ethyl orthoformate. Equimolecular amounts of diacetyl and ethyl orthoformate reacted exactly as above to give, after fractionation, 3 : 3-diethoxybutan-2-one (yield, 47·5%), b. p. 66·5—67·5°/20 mm. (Found: C, 59·4; H, 9·9%; *M* (cryoscopic in benzene), 166; n_D^{25} 1·4033; d_4^{25} 0·9217; $[R_L]_D$ 42·39. Calc. for $C_8H_{16}O_3$: C, 60·0; H, 10·0%; *M*, 160; $[R_L]_D$ 42·44).

By refractionation of the lower-boiling component, fractions were obtained which gave absorption bands at 250 mμ., the fraction in which this band was most pronounced having $E_{1cm.}^{1\%}$ 10·1 at $\lambda_{max.}$ 250 mμ.

Reaction of 3 : 3-*diethoxybutan-2-one with hydroxylamine and semicarbazide.* The ketone was added to an aqueous solution of hydroxylamine hydrochloride containing sodium acetate and heated. The oxime separated out as colourless crystals, m. p. 233° (after recrystallisation from dilute alcohol) not depressed in admixture with dimethylglyoxime, m. p. 235°.

Reaction with semicarbazide hydrochloride and sodium acetate gave colourless crystals, m. p. 276° (after recrystallisation from glacial acetic acid) not depressed in admixture with diacetyl disemicarbazone, m. p. 279°.

Thanks are due to Mr. F. W. G. Schöning for carrying out the microanalyses and to the South African Council for Scientific and Industrial Research for permission to publish this note.—National Chemical Research Laboratory, Pretoria, South Africa. [*Received, April 25th*, 1950.]

The Reaction of Some Sulphonazides with Pyridine. By G. L. Buchanan and R. M. Levine.

The reaction of sulphonazides (I) with pyridine was first studied by Curtius (*J. pr. Chem.*, 1930, **125**, 303) who formulated the products as sulphonamides of type (II). In no case did he prove the structure, although he demonstrated that on hydrolysis they yielded the corresponding sulphonic acid and a basic material which had the composition of an aminopyridine. In one such case (R = β-naphthyl)

R·SO$_2$·N$_3$ (I.) R·SO$_2$·NH·C$_5$H$_4$N (II.) ⊖N·SO$_2$·R (III.) NH$_2$ X⊖ (IV.)

the base gave a picrate and a platinichloride closely resembling those of 2-aminopyridine, but the identity was not tested.

More recently, Ashley, Buchanan, and Easson (*J.*, 1947, 60) and Datta (*J. Indian Chem. Soc.*, 1947, **24**, 109) have proved that *p*-acetamidobenzene- (I; R = *p*-NHAc·C$_6$H$_4$·) and toluene-*p*-sulphonazide (I; R = *p*-C$_6$H$_4$Me·) give condensation products of type (III) which are hydrolysed to salts (IV) of the unstable free base.

These results suggest that the reaction does not always follow the same course. We have confirmed the results reported by Curtius for two azides (I; R = Ph and *p*-C$_6$H$_4$Cl) but not for (I; R = β-C$_{10}$H$_7$). The products are insoluble in alkali and yield, on hydrolysis, the appropriate sulphonic acid and 1-aminopyridinium salts (IV). We have also confirmed that no rearrangement has occurred during the hydrolysis of the β-naphthyl compound by re-synthesising 1-(naphthalene-β-sulphonimido)pyridine (III; R = β-C$_{10}$H$_7$) from the hydrochloride (IV; X = Cl) and naphthalene-β-sulphonyl chloride.

These results establish the point of attachment to the pyridine nucleus. Hence the condensation product are of type (III).

Experimental.—Pyridine was previously redistilled and dried over potassium hydroxide pellets, although we have no reason to believe this to have been necessary. The azides were prepared in 83—89% yield from the corresponding sulphonyl chlorides and sodium azide, by the aqueous acetone method described by Ashley *et al.* (*loc. cit.*). Condensations were effected as described by Curtius except where otherwise stated. Hydrolysis products or their salts were identified by mixed m. p. determinations.

1-Benzenesulphonimidopyridine (III; R = Ph), prepared from the azide (90 g.) and pyridine (1·5 l.) and recrystallised from methanol, had m. p. 152° (36 g.) and gave a hydrochloride, m. p. 198—200°. Although isolation (cf. Curtius) involves dissolving the tarry crude product in alkali and reprecipitating it with acid, the pure product is not soluble in alkali, but dissolves in acids. The anomalous properties of the tar must be due to acidic by-products (see Ashley *et al.*, *loc. cit.*) and the solvent action of residual pyridine.

1-(*p*-Chlorobenzenesulphonimido)pyridine (III; R = *p*-C$_6$H$_4$Cl·) was prepared by boiling the azide (85 g.) and pyridine (1·5 l.) for 48 hours. The excess of pyridine was distilled off under reduced pressure, and the dark residual tar treated with methanol. Next morning, the product which had crystallised was recrystallised from alcohol, forming colourless prisms, m. p. 182° (40 g.) (Found: C, 48·9; H, 3·4; N, 10·4. C$_{11}$H$_9$O$_2$N$_2$SCl requires C, 49·2; H, 3·35; N, 10·4%), insoluble in alkali, but soluble in acid, and yielding a picrate m. p. 192°.

1-(Naphthalene-β-sulphonimido)pyridine (III; R = β-C$_{10}$H$_7$), prepared from the azide (90 g.) and pyridine (1·5 l.) at the b. p. (72 hours), was isolated as described above for the *p*-chloro-compound. Recrystallisation from water yielded colourless crystals, m. p. 197—198° (23 g.), soluble in acids but insoluble in alkali and yielding a picrate, m. p. 199—200° (Curtius gives 192°).

Hydrolysis of 1-*benzenesulphonimidopyridine.* The conditions successfully employed by Ashley *et al.* (*loc. cit.*), namely boiling for a few hours with *ca.* 6*N*-hydrochloric acid, were ineffective.

The substance (1 g.) in concentrated hydrochloric acid (15 c.c.) was heated at 150° for 2½ hours. Evaporation on the steam-bath then yielded a hygroscopic product, m. p. 110°, probably the crude benzenesulphonate described by Curtius as having m. p. 115°, but an attempt to free the base with alkali led to darkening and liberation of pyridine. This would be difficult to explain if the base were 2-, 3-, or 4-aminopyridine, but agrees with the properties of 1-aminopyridinium salts, as described by Ashley *et al.* (*loc. cit.*). The hygroscopic sulphonate yielded 1-aminopyridinium picrate [IV; X = O·C$_6$H$_2$(NO$_2$)$_3$], m. p. 152°, and *S*-benzylthiuronium benzenesulphonate, m. p. 146°.

Hydrolysis of 1-(*p-chlorobenzenesulphonimido*)*pyridine.* The conditions described above were necessary and the base could not be isolated by treatment with alkali. It was identified as 1-aminopyridinium picrate, m. p. 152°. The *p*-chlorobenzenesulphonic acid was identified as its *S*-benzylthiuronium salt, m. p. 173—174°.

Hydrolysis of 1-(*naphthalene-β-sulphonimido*)*pyridine.* In order to confirm that no rearrangement occurs under the conditions of hydrolysis, this was carried out in three ways. The second and third correspond to those employed by Curtius (*loc. cit.*).

(*a*) The compound (5 g.) in hydrochloric acid (45 c.c.; *ca.* 8*N*.) was refluxed for 4½ hours. On cooling, naphthalene-β-sulphonic acid separated and was identified as its *S*-benzylthiuronium salt, m. p. 188—189°. The filtrate was concentrated on the steam-bath, to a syrup, and treated with aqueous picric

acid, yielding 1-(naphthalene-β-sulphonimido)pyridine picrate, m. p. 199—200°, and the mother-liquors therefrom gave 1-aminopyridinium picrate, m. p. 152°.

(*b*) The compound (5 g.) in concentrated hydrochloric acid (40 c.c.) was boiled for 12 hours. Naphthalene-β-sulphonic acid crystallised out and was identified as above. A portion of the filtrate was concentrated to a syrup and triturated with alcohol. The resulting 1-aminopyridinium chloride, recrystallised from alcohol, had m. p. 158—160°. The remainder of the filtrate was treated with aqueous picric acid; in spite of Curtius's claim to have isolated a picrate of m. p. 216—217°, we isolated only 1-aminopyridinium picrate, m. p. 152°.

(*c*) The compound (5 g.) in concentrated hydrochloric acid (20 c.c.) was heated at 125° for 7 hours. Naphthalene was isolated in almost quantitative yield. The filtrate, concentrated to a syrup and treated with aqueous picric acid, gave only 1-aminopyridinium picrate, m. p. 152°.

Re-synthesis of 1-(*naphthalene-β-sulphonimido*)*pyridine.* To naphthalene-β-sulphonyl chloride (1·7 g.) in acetone (5 c.c.) there were added 1-aminopyridinium chloride (1 g.) in water (2 c.c.), and then solid potassium carbonate till the solution was alkaline, and further amounts of carbonate, water, and acetone till a homogeneous solution was obtained. This was shaken for some time and left overnight. The acetone was removed. The solid product which separated was recrystallised from alcohol and then had m. p. 198° (1·5 g.), alone or when mixed with the reaction product described above. The picrates, m. p. 199—200°, were similarly shown to be identical, and the synthetic material gave a nitrate of m. p. 156—157°, which agreed with that quoted by Curtius (*loc. cit.*).

The micro-analysis was carried out by Miss R. H. Kennaway.—University of Glasgow. [*Received, May 4th*, 1950.]

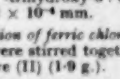
Reactions of Ferric Chloride with o- *and* p-*Cresol.* By K. Bowden and C. H. Reece.

With ferric chloride α- and β-naphthol have long been known to give dinaphthols (Dianin, *J. Russ. Phys. Chem. Soc.*, 1874, **6**, 183). The action of the same reagent on simple phenols not containing a bicyclic system but having a methyl group in the *ortho*- or the *para*-position has now been examined.

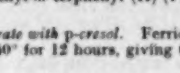
Anhydrous ferric chloride, or ferric chloride hexahydrate, with *p*-cresol under mild conditions gives the diphenyl derivative (I) and the terphenyl derivative (II). In a dilute aqueous solution the compound (I) is formed, together with a neutral compound to which Pummerer *et al.* (*Ber.*, 1925, **58**, 1808) assigned the structure (III) (cf. Westerfield and Lowe, *J. Biol. Chem.*, 1942, **145**, 463). There was no reaction between ferric chloride and *p*-cresol in 10% hydrochloric acid.

o-Cresol with ferric chloride hexahydrate or an ethereal solution of anhydrous ferric chloride gave a polyphenol of unknown constitution.

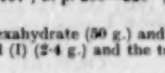
Experimental.—Reaction of anhydrous ferric chloride with p-*cresol.* *p*-Cresol (21 g.) and anhydrous ferric chloride (35 g.) were stirred together at 30° for 12 hours, hydrogen chloride being evolved. The product was extracted with benzene (100 c.c.), and the extract washed with dilute hydrochloric acid,



(I.)



(II.)



(III.)

dried (Na_2SO_4), and distilled under reduced pressure to give unchanged *p*-cresol (13·1 g.), 2 : 2′-dihydroxy-5 : 5′-dimethyldiphenyl (I) (2·2 g.), m. p. 154°, b. p. 160—175° (air-bath temp.)/10^{-4} mm., and 2 : 2′ : 2″-trihydroxy-5 : 5′ : 5″-trimethyl-*m*-terphenyl (II) (1·2 g.), m. p. 197°, b. p. 200—220° (air-bath temp.)/2×10^{-4} mm.

Reaction of ferric chloride hexahydrate with p-*cresol.* Ferric chloride hexahydrate (50 g.) and *p*-cresol (21 g.) were stirred together at 35—40° for 12 hours, giving the diphenyl (I) (2·4 g.) and the terphenyl derivative (II) (1·9 g.).

Reaction of ferric chloride with p-*cresol in dilute aqueous solution.* *p*-Cresol (21 g.) and ferric chloride hexahydrate (65 g.) in water (3 l.) were stirred together for 4 hours at 20°, the solution changing from orange to green. A white precipitate which formed was filtered off and dissolved in ether, and the ethereal solution extracted with 5% sodium hydroxide solution (100 c.c.). After being dried (Na_2SO_4), the ethereal solution was evaporated, to give a solid (III) which crystallised from alcohol as colourless plates, m. p. 128° (0·3 g.) (Found: C, 78·7; H, 6·4. Calc. for $C_{14}H_{14}O_2$: C, 78·5; H, 6·5%). The compound gave an oxime, m. p. 195° (cf. Pummerer *et al.*, *Ber.*, 1922, **55**, 3116). On acidification of the alkaline extract the diphenyl derivative (I) was obtained which, crystallised from *cyclo*hexane, had m. p. 154° (1·1 g.).—The University, Leeds, 2. [*Received, May 5th*, 1950.]

The Conversion of Aromatic Aldehydes into Primary Amines by a Simple Adaptation of the Leuckart Reaction. By K. G. Lewis.

The Leuckart reaction was first discovered in the reaction of benzaldehyde with formamide or ammonium formate and yielded mainly tribenzylamine with a trace of benzylamine. In its subsequent application the reaction has found its principal use in the formation of primary amines from ketones of various types. During application of the reaction to various simple alicyclic ketones conditions were found

that markedly improved the yields of primary amine; *e.g.*, *cyclo*hexylamine was obtained from *cyclo*hexanone in 75% yield.

In view of recent statements (Moore, "The Leuckart Reaction" in "Organic Reactions," Vol. V, Wiley and Sons, New York, 1949, and Angyal and Rassack, *Nature*, 1948, **161**, 723) in regard to the non-formation of primary amines from aromatic aldehydes by this reaction, it was considered of interest to apply to these substances the conditions so successful with *cyclo*hexanone.

The modified Leuckart reaction, applied to various available aromatic aldehydes and to furfuraldehyde, gave the corresponding primary amines of the benzylamine type in yields ranging from 62 to 15%. In agreement with the work of Crossley and Moore (*J. Org. Chem.*, 1944, **9**, 529) it was found that hydrolysis of the whole reaction mixture, and not only of the extracted crude formyl derivative, led to improved yields: *e.g.*, benzylamine, 60% compared with 43%; *cyclo*hexylamine, 75% compared with 40%.

Experimental.—The general procedure used was as follows: The aldehyde (0·1 mol.) was added drop-wise with shaking to 50 g. (0·8 mol.) of ammonium formate (or the corresponding amount of ammonium formate–formamide reagent prepared according to Ingersoll, *J. Amer. Chem. Soc.*, 1936, **58**, 1809) at 165°. The reaction was carried out in a three-necked flask to which was attached a short column connected for distillation. The reaction temperature was raised as soon as possible to 185—190° and maintained in this range while the remainder of the aldehyde was added. Initially some of the aldehyde distilled, but as the reaction proceeded it largely reacted without loss. The aldehyde that distilled was recovered and returned to the reaction mixture. The addition required 30—40 minutes in most cases and the reaction was substantially complete in about 3 hours at 185—190° (including the time of addition). The reaction mixture was cooled, concentrated hydrochloric acid (100 ml.) added, the mixture refluxed for 2 hours, then made strongly alkaline, and the amine steam-distilled into hydrochloric acid. This solution was evaporated, the residue was made alkaline and the amine recovered by extraction and distillation.

The amines which were prepared and the yields obtained are set out in the Table. The derivatives were prepared by standard procedures and the m. p.s agreed with those recorded in the literature.

Amine.	Yield, %.	B. p./680 mm.	Derivatives (m. p.s, uncorr.; d. = decomp.).
Benzylamine	60	180—182°	Picrate, 197—198°; *N*-benzoyl, 105°.
p-Methylbenzylamine	62	198—200	Picrate, 205° d.; *N*-benzoyl, 137—138°.
o-Methoxybenzylamine ...	30	218—220	Hydrochloride, 150°; *N*-acetyl, 96—97°.
p-Methoxybenzylamine ...	23	232—234	Picrate, 188°; *N*-acetyl, 96°.
m-Nitrobenzylamine [1]	41	—	Hydrochloride, 224°; nitrate, 182—183°.
Furfurylamine [2]	15	140—142	Picrate, 183—184° d.; oxalate, 145—147°.

[1] *m*-Nitrobenzaldehyde was added to the reaction mixture dissolved in nitrobenzene; the amine was isolated as the hydrochloride. [2] In this case the crude formyl derivative was isolated and hydrolysed with 30% sodium hydroxide.

Acknowledgment is made to the Commonwealth Science Research Fund for financial assistance.—
New England University College, Armidale, N.S.W., Australia. [*Received, May 22nd*, 1950.]

A Note on the Isomeric Benzoate–Toluene-p-sulphonates of Propylene Glycol. By G. A. Haggis and L. N. Owen.

The opening of the epoxide ring in propylene oxide under various conditions has been studied by many investigators (*inter al.*, Petrov, *J. Gen. Chem. Russia*, 1944, **14**, 1038; Chitwood and Freure, *J. Amer. Chem. Soc.*, 1946, **68**, 680; Swern, Billen, and Knight, *ibid.*, 1949, **71**, 1152; Reeve and Sadle, *ibid.*, 1950, **72**, 1251), and it has generally been found that under acid conditions ring-opening occurs in both of the possible directions to give a mixture of the primary and secondary products:

$$CH_2\text{-}\overset{\diagup O \diagdown}{CH}\text{-}CH_3 + HX \longrightarrow CH_2\text{-}CH(OH)\text{-}CH_2X + CH_2\text{-}CHX\text{-}CH_2\text{-}OH$$

Chapman and Owen (*J.*, 1950, 579) found that by treatment of propylene oxide with toluene-*p*-sulphonic acid in dry ether, followed by benzoylation of the product, a mixture of the two isomeric benzoate–toluene-*p*-sulphonates of the diol was obtained, from which, by fractional crystallisation, 2-toluene-*p*-sulphonyloxypropyl benzoate, m. p. 104°, was isolated. The residual material, m. p. 79°, was shown to be a mixture of this compound with 1-toluene-*p*-sulphonyloxyprop-2-yl benzoate, but fractional crystallisation failed to effect any further separation. In a renewed investigation of this mixture, we have now found that by slow crystallisation from light petroleum two distinct types of crystals are formed, and pure 1-toluene-*p*-sulphonyloxyprop-2-yl benzoate, m. p. 93°, has thereby been obtained. Both compounds have also been prepared by selective esterification of propylene glycol.

It has already been shown (Chapman and Owen, *loc. cit.*) that the two isomers differ in their rates of reaction with potassium thiolacetate; this has now been found to be the case also with sodium iodide. Furthermore, the product thus formed from the compound of m. p. 104° is 2-iodopropyl benzoate, since on hydrogenation it furnishes *n*-propyl benzoate; this provides rigid proof of the structures.

Reaction of propylene oxide in aqueous solution with benzoic acid and potassium benzoate gave mainly (but not exclusively) the primary benzoate of propylene glycol, since the product, on toluene-*p*-sulphonation, consisted largely of the benzoate–toluene-*p*-sulphonate m. p. 104°. According to Fraenkel-Conrat and Olcott (*J. Amer. Chem. Soc.*, 1944, **66**, 1420), carboxylic acids react with propylene

oxide under these conditions to give only the primary esters, but their evidence is open to criticism. It is stated, for instance, that the compound obtained when the reaction is carried out with butyric acid is the pure 1-butyrate because it is identical (in refractive index) with that prepared by the reaction of sodium butyrate with 1-chloropropan-2-ol; since, however, a rearranged product (derived *via* a cyclic intermediate) may well be formed in the latter reaction, deduction of structure by such means is clearly unwarranted (compare Ross, *J.*, **in the press**).

Toluene-p-sulphonyloxypropyl Benzoates.—Propylene oxide was treated with toluene-*p*-sulphonic acid in dry ether, and the product was benzoylated, according to the procedure of Chapman and Owen (*loc. cit.*). Fractional crystallisation of the crude material from benzene–light petroleum (b. p. 60—80°) gave, as before, 2-toluene-*p*-sulphonyloxypropyl benzoate, m. p. 104°, and the mixture of isomers, m. p. *ca.* 79°. Slow crystallisation of this mixture from a dilute solution in light petroleum (b. p. 60—80°) gave a mixture of plates and needles. By careful warming and stirring, the needles were found to redissolve in the supernatant liquid more readily than the plates; the latter were then collected and were substantially pure 2-toluene-*p*-sulphonyloxypropyl benzoate, m. p. 101—103°, raised to 103—104° after one recrystallisation. Concentration of the mother-liquors, and repetition of the process several times, eventually resulted in the deposition of needles only; recrystallisation of this material from methanol then gave needles of *1-toluene-p-sulphonyloxyprop-2-yl benzoate*, m. p. 93° (Found: C, 61·0; H, 5·45; S, 9·25. $C_{17}H_{18}O_5S$ requires C, 61·05; H, 5·4; S, 9·6%). Mixed m. p. determinations with various proportions of the isomers gave the following results:

Secondary benzoate, %	0	10	20	29	43
M. p.	104°	90—100°	80—95°	77—85°	76—80°
Secondary benzoate, %	50	57	75	90	100
M. p.	76—78°	76—78°	76—79°	80—86°	93°

Monoesterification of Propylene Glycol.—(i) Propylene glycol (5 g.) was dissolved in pyridine (100 c.c.) and the solution was cooled to 0°. A solution of toluene-*p*-sulphonyl chloride (12·5 g., 1·05 mols.) in pyridine (50 c.c.) was added in portions of 0·5 c.c. during 4 days. After removal of most of the pyridine under reduced pressure, the residue was taken up in chloroform and washed with dilute sulphuric acid, sodium hydrogen carbonate solution, and finally with water. After being dried (Na_2SO_4), the solvent was removed to give a brown viscous oil (5·9 g.) n_D^{20} 1·5135, which was dissolved in pyridine (30 c.c.), cooled to 0°, and treated with benzoyl chloride (7 g.). After 2 hours the solution was poured into water and worked up as above to give a dark oil which partly crystallised on addition of light petroleum. The crude solid was collected and recrystallised from methanol to give 1-toluene-*p*-sulphonyloxyprop-2-yl benzoate (1·9 g.), m. p. 92—93°, identical with that obtained previously.

(ii) Propylene glycol (5 g.) was dissolved in pyridine (50 c.c.) and cooled to 0°. A solution of benzoyl chloride (8·25 g.; 1·04 mols.) in pyridine (100 c.c.) was added in 0·5-c.c. portions during 4 days. Working up as above gave an oil, which on distillation gave propylene glycol monobenzoate (1·8 g.), b. p. 93—97°/2 mm., n_D^{20} 1·5229. Reaction of this oil with toluene-*p*-sulphonyl chloride (2·1 g.) in pyridine (15 c.c.) gave a product which on crystallisation from benzene–light petroleum (b. p. 60—80°) gave a main crop (1·2 g.) of 2-toluene-*p*-sulphonyloxypropyl benzoate, m. p. 104°.

Reactivity towards Sodium Iodide.—Each of the isomeric compounds (0·1 g.) was separately treated under identical conditions with a boiling solution of sodium iodide (0·15 g.) in acetone (6 c.c.) for 2½ hours under reflux. The solutions were cooled and filtered, and the precipitated sodium toluene-*p*-sulphonate was washed with cold acetone (5 c.c.) and dried. The yields (uncorrected for slight solubility in acetone) were: from the primary toluene-*p*-sulphonate, 0·028 g. (48%); from the secondary, 0·005 g. (9%).

2-Iodopropyl Benzoate.—2-Toluene-*p*-sulphonyloxypropyl benzoate (20 g.) in acetone (240 c.c.) containing sodium iodide (20 g.) was heated under reflux for 20 hours; precipitation of sodium toluene-*p*-sulphonate began after 30 minutes. The solid was filtered off, washed with acetone, and dried (Yield, 10·7 g.; calc., 10·8 g.). Acetone was removed from the filtrate by distillation, and water was added to the residue. The oil was extracted into light petroleum (b. p. 40—60°) and washed with aqueous sodium thiosulphate and with water. After drying (Na_2SO_4) and removal of solvent, distillation gave *2-iodopropyl benzoate* as a pale yellow oil (13·2 g.), b. p. 96—98°/0·3 mm., n_D^{18} 1·5668 (Found: C, 40·9; H, 3·7; I, 45·8. $C_{10}H_{11}O_2I$ requires C, 41·4; H, 3·82; I, 43·75%). The slight discrepancy in analysis may be due to the formation of a trace of propylene di-iodide by replacement of the benzoate group.

Hydrogenation of 2-Iodopropyl Benzoate.—The ester (12·6 g.) was dissolved in methanol (160 c.c.) containing potassium acetate (5 g.) and hydrogenated at atmospheric pressure over Adams's platinum catalyst (0·4 g.). When uptake was complete the catalyst was filtered off, the solvent removed by distillation, and water added to the residue. The ester was extracted with light petroleum (b. p. 40—60°) and dried (Na_2SO_4). After removal of solvent, distillation gave *n*-propyl benzoate, b. p. 105—110°/13 mm., n_D^{19} 1·4994 (lit., n_D^{20} 1·5000). This was hydrolysed with aqueous 10% potassium hydroxide, and the resulting alcohol was characterised (*a*) as *n*-propyl 3 : 5-dinitrobenzoate, m. p. and mixed m. p. 72°, and (*b*) by oxidation with chromic acid and formation of propaldehyde 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 152°.

Reaction of Propylene Oxide and Benzoic Acid. (With J. H. Chapman.)—Propylene oxide (40 g.) was dissolved in water (400 c.c.) containing potassium hydroxide (1·0 g.). Benzoic acid (20 g.) was added, followed by sufficient acetone (*ca.* 150 c.c.) to give a homogeneous solution; after 5 days, a further 40 g. of propylene oxide were added. At the end of a further 5 days the solution was still acidic. Acetone was removed under reduced pressure and the aqueous solution was neutralised with sodium hydrogen carbonate and extracted with ether. The extract was dried (Na_2SO_4), concentrated, and distilled to give the benzoate as a colourless oil, b. p. 105—111°/0·4 mm., n_D^{19} 1·5170—1·5213 (9·8 g.).

This was treated in pyridine (50 c.c.) with toluene-*p*-sulphonyl chloride (11·7 g.), and gave a solid (14 g.), m. p. 75—95°, which by two recrystallisations from methanol gave 2-toluene-*p*-sulphonyloxypropyl benzoate (8 g.), m. p. and mixed m. p. 104°.—IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY, SOUTH KENSINGTON, LONDON, S.W.7. [*Received, May 25th*, 1950.]

The Addition of Osmium Tetroxide to Dinaphthylethylenes. By C. A. COULSON.

IN a recent letter to *Nature* having the same heading as this note, Badger (*Nature*, 1950, **165**, 647) has shown experimentally that osmium tetroxide adds to the three *cis*- and *trans*-dinaphthylethylenes at a rate $\beta\beta > \alpha\beta > \alpha\alpha$. It has generally been presumed that, other things being equal, the rate of addition depended on the double-bond character of the bond to which the addition occurs—here the central ethylene link. This presumption would receive further support if it could be shown that the bond orders were also in the sequence $\beta\beta > \alpha\beta > \alpha\alpha$. Badger gives reasons why this is likely to be so. The argument depends on the known greater conjugating power (Coulson and Longuet-Higgins, *Proc. Roy. Soc.*, 1948, *A*, **195**, 188) of naphthalene at the α- than at the β-position; but no absolute calculations of the bond order have hitherto been made. For that reason the three bond orders have now been calculated, and are shown below. Standard molecular-orbital technique was used, with numerical integration as in some earlier work (Coulson and Jacobs, *J.*, 1949, 2805). The values are: $\beta\beta$ 1·814, $\alpha\beta$ 1·803, $\alpha\alpha$ 1·792. The sequence is precisely what was expected, the differences between the three values being of the same order of magnitude as those commonly found (Berthier, Coulson, Greenwood, and Pullman, *Compt. rend.*, 1948, **226**, 1906) in polynuclear hydrocarbons, the addition of osmium tetroxide to which has been studied fairly fully (cf. Badger, *J.*, 1949, 456). To this extent, then, the present calculations provide further support for the general interpretation of this addition reaction.

It may be worth comparing the values for the ethylenic bond orders in the dinaphthylethylenes with the value in stilbene (1·820). Thus the replacement of two phenyl by two naphthyl groups increases the conjugation over the whole molecule and therefore weakens the central bond. A similar situation was fully discussed in a variety of other systems by Coulson and Jacobs (*loc. cit.*).—WHEATSTONE PHYSICS LABORATORY, KING'S COLLEGE, LONDON. [*Received, May 23rd*, 1950.]

6-Ethyl-1 : 3-dimethylnaphthalene and 1-Ethyl-1 : 2 : 3 : 4-tetrahydro-5-hydroxy-7 : 8-dimethylnaphthalene. By WESLEY COCKER and BRIAN E. CROSS.

6-ETHYL-1 : 3-DIMETHYLNAPHTHALENE has been prepared from 7-ethyl-1 : 2 : 3 : 4-tetrahydro-1-keto-2 : 4-dimethylnaphthalene (Cocker *et al.*, *J.*, 1950, in the press) by Clemmensen reduction to the tetralin, followed by dehydrogenation with palladised charcoal. The naphthalene was characterised as its picrate and its trinitrobenzene and trinitrotoluene adducts.

Catalytic hydrogenation of 1-ethyl-3 : 4-dihydro-5-methoxy-7 : 8-dimethylnaphthalene (Cocker, *et al.*, *loc. cit.*) followed by demethylation yielded 1-ethyl-1 : 2 : 3 : 4-tetrahydro-5-hydroxy-7 : 8-dimethylnaphthalene.

Experimental.—*6-Ethyl-1 : 3-dimethylnaphthalene.* *6-Ethyl-1 : 2 : 3 : 4-tetrahydro-1 : 3-dimethylnaphthalene* (Found: C, 89·05; H, 10·35. $C_{14}H_{20}$ requires C, 89·4; H, 10·6%) was obtained as a colourless liquid (1·4 g.), b. p. 128—129°/10 mm., when 7-ethyl-1 : 2 : 3 : 4-tetrahydro-1-keto-2 : 4-dimethylnaphthalene (Cocker *et al.*, *loc. cit.*) (2·3 g.) was refluxed for 40 hours with amalgamated zinc (70 g.), concentrated hydrochloric acid (90 c.c.), and water (50 c.c.).

The tetralin (1·0 g.) was heated with palladised charcoal (0·9 g.) at 250—270° for 5 hours. The product was extracted with ether and distilled over sodium, yielding the *naphthalene* (0·84 g.), b. p. 148—150°/10 mm. (Found: C, 91·1; H, 9·1. $C_{14}H_{14}$ requires C, 91·3; H, 8·7%). Its *picrate* crystallised from methanol as rosettes of orange needles, m. p. 70° (Found: C, 58·1; H, 5·0. $C_{20}H_{17}O_7N_3$ requires C, 58·1; H, 4·6%). Its *trinitrobenzene* derivative crystallised from methanol as lemon-yellow needles, m. p. 97° (Found: C, 60·8; H, 4·8. $C_{26}H_{19}O_6N_3$ requires C, 60·45; H, 4·8%). Its *trinitrotoluene* adduct crystallised from methanol as lemon-yellow needles, m. p. 43·5° (Found: C, 61·2; H, 5·15. $C_{27}H_{21}O_6N_3$ requires C, 61·3; H, 5·1%).

1-Ethyl-1 : 2 : 3 : 4-tetrahydro-5-hydroxy-7 : 8-dimethylnaphthalene. 1-Ethyl-3 : 4-dihydro-5-methoxy-7 : 8-dimethylnaphthalene (Cocker *et al.*, *loc. cit.*) (3·33 g.) and palladised charcoal (2·0 g.) in ethyl acetate (50 c.c.) were shaken in hydrogen, giving the methoxy-tetralin (3·08 g.), b. p. 147—150°/6 mm. The methoxy-compound was refluxed for 2 hours with redistilled hydriodic acid (12 c.c.) and glacial acetic acid (15 c.c.). The *hydroxy*-compound, b. p. 146—152°/6 mm., crystallised from light petroleum (b. p. 40—60°); m. p. 59—60° (Found: C, 82·05; H, 9·55. $C_{14}H_{20}O$ requires C, 82·35; H, 9·8%).—CHEMICAL LABORATORY, TRINITY COLLEGE, DUBLIN. [*Received, June 6th*, 1950.]

OBITUARY NOTICE.

SIR ROBERT PICKARD.

1874—1949.

The death of Sir Robert Pickard on October 18th, 1949, at the age of 75 brought to a close a notable career of varied interests and removed from our midst a strong and vigorous personality whose impress has been left on several spheres of activity in science, technology, and education.

Robert Howson Pickard, born at Balshall Heath, Birmingham, on the 27th September, 1874, was the elder of the two sons of Joseph Henry Pickard, a tool manufacturer in Birmingham, and of Alice, daughter of Robert Howson of Birmingham.

He received his schooling at King Edward's Grammar School, Camp Hill, Birmingham, which he attended from 1883 to 1891, and where he was one of the pupils of the gifted headmaster, the Reverend Jamson Smith.

From 1891 to 1895 he was a student at Mason University College and obtained the B.Sc. degree of London University in 1895 with first class honours in Chemistry. At the time of Tilden's departure from Mason College for the Royal College of Science in 1894, Pickard was senior student and secretary of the students' Chemical Society, and in the following year he became President of the Union and also a post-graduate student under the new professor, P. F. Frankland. To both these distinguished teachers Pickard at different times acknowledged his great indebtedness.

Pickard was always a keen sportsman and at Camp Hill was Captain of School Cricket in 1890—91 and later played both cricket and rugby for Mason College.

In January 1896 he proceeded as an "1851 Exhibitioner" to the University of Munich, where, under the direction of Thiele, he carried out research work concerned principally with the rearrangement of hydroxamic acids and in June 1898 obtained the degree of Ph.D. *summa cum laude*. The results of this investigation were published in *Annalen* and *Berichte*. He then returned to Birmingham and spent another year divided between chemical research and bacteriology. He was awarded the D.Sc. of London University in 1899.

In July, 1899, Pickard received his first appointment, that of Head of the Chemistry Department of Blackburn Technical School. He set about with characteristic energy and industry to improve the laboratories and extend the facilities for the teaching of chemistry, so that the students attending this provincial technical school were enabled to prepare for the external degrees of the University of London. In a relatively short time research work was started in collaboration with members of his staff and subsequently with senior students.

Pickard's main interest as a chemist lay in stereochemistry and particularly in the relation between chemical constitution and optical rotatory power. Apart from his work in Munich, his first scientific publication was a joint one with Frankland on "The Rotation of Optically Active Compounds in Organic Solvents" and there can be little doubt that this, together with Frankland's influence, gave the general direction to Pickard's chemical interests.

One of his earlier investigations involved an attempt to resolve racemic alcohols into their optically active forms by combining them with either menthyl or bornyl *iso*cyanate and submitting the resulting urethanes to fractional crystallisation. The method however proved unsatisfactory, as hydrolysis of the optically active urethanes could only be effected under conditions which resulted in the liberated alcohols being partly racemised.

Shortly afterwards, in collaboration with his colleagues at Blackburn, he devised a method of resolving racemic secondary alcohols into their optically pure isomerides which proved both convenient and of general application. The alcohols are converted, by reaction with the anhydride of a dibasic acid, usually phthalic or succinic, into acid esters which form with the commoner alkaloids crystalline salts of sufficient stability to allow of their separation into diastereoisomeric forms by fractional crystallisation. The derived optically active acid esters readily undergo hydrolysis under mild conditions and yield the liberated alcohols in a condition of optical purity. This method is of such practical convenience as to allow of the ready preparation of optically active alcohols in relatively large amounts and has thus put at the service of chemists a means of obtaining optically active and chemically reactive compounds of simple constitution for a wide variety of purposes.

By application of this procedure the four borneols, (+)- and (−)-borneol and (+)- and (−)-*iso*borneol, and the four menthols, (+)- and (−)-menthol and (+)- and (−)-*iso*menthol, were readily prepared and a comparison was made of their rotatory powers.

The same method was also used to prepare a number of homologous series of optically active

alcohols and of their esters in order to study the effect, on rotatory power, of a growing chain in alcohols of the structure CHRR'·OH where R and R' could be independently varied and in carboxylic esters of the structure R''·CO·O·CHRR' where R, R', and R'' may be similarly changed. The rotatory powers of these groups of compounds were determined, with light of different wave-lengths, both for the homogeneous state at different temperatures and for solutions in various solvents at different concentrations.

The main conclusions drawn from this lengthy and laborious investigation were:

(i) Compounds of simple chemical constitution containing an unbranched chain of five (or ten) carbon atoms may exhibit an enhanced rotatory power—this effect, in all probability, being due to the chain of five carbon atoms all but returning on itself.

(ii) This normal chain of five (or ten) carbon atoms need not be directly attached to the asymmetric carbon atom, but when indirectly attached the disturbing influence is much less pronounced.

(iii) This special stereochemical influence of the chain of atoms is usually increased by the action of solvents and in some cases where the influence is latent in homogeneous liquids it can become quite pronounced in solution.

(iv) The molecular rotatory powers of the members of a homologous series of compounds alter (usually increase) in a continuous manner as the series is ascended, rapidly at first, and then much more slowly, so that they tend towards a constant value.

(v) The rotatory powers of a whole group of optically active compounds of closely related chemical constitutions and of their derivatives can be correlated by an extension of the "characteristic diagram" method devised by Armstrong and Walker (*Proc. Roy. Soc.*, **1903**, ***A***, **88**, 338).

These results, together with some others dealing with the rotatory powers of menthyl carbamates and menthyl carbamides, were discussed in an appreciative manner by Professor P. F. Frankland in his Presidential Address on "Some Stereochemical Problems" delivered to the Chemical Society in **1912**, an action which gave much pleasure to his old student Pickard.

Pickard was elected to the Fellowship of the Royal Society in **1917** whilst still at Blackburn, in itself a notable achievement and a great honour to a provincial technical school.

He published a few more papers on these topics after moving to Battersea Polytechnic but gradually his administrative and other duties drew him away from participation in purely chemical subjects, although he always liked to assume a paternal attitude to the activities of the Chemistry Department which he visited whenever he had a few moments to spare.

From **1908** to **1920** he combined the duties of Head of the Chemistry Department with those of Principal of the Technical School at Blackburn, and thus found wider opportunities for the exercise of his developing administrative abilities.

During this period he was from time to time consulted by cotton manufacturers of the surrounding district on various problems and difficulties encountered in this local industry, and it is certain that he came to see quite clearly that the application of more scientific methods to this complex industry would result in great improvements to many processes which at that period were carried out by empirical and indeed rough rule-of-thumb methods. This experience undoubtedly laid the foundation of the very real and lively interest which he developed and the extensive technical knowledge which he gradually acquired, both of which he was later to put to such good and effective use during his Directorship of the British Cotton Industry Research Association at the Shirley Institute.

From **1900** to **1920** Pickard was consultant chemist to the Corporation of Blackburn with the duties of examining the supplies of water and gas and the town's sewage effluent.

Early in **1920**, Pickard was appointed Principal of Battersea Polytechnic, a position he held with marked success until **1927**. During this period he fostered more advanced studies and his vision and determination greatly helped to widen and encourage the University side of the Polytechnic's teaching activities during those difficult post-war years. There is little doubt that the general life of the Polytechnic was stimulated by his presence and capable supervision. He mixed freely with students of all departments and played a vigorous game of badminton with members of his staff, and a less vigorous game of cricket with students.

As Pickard's interests and activities were widely spread it has seemed most convenient to deal with these in separate sections.

Services to the University of London.—In **1926** Pickard became a member of the Senate of the University of London and remained so for **22** years until failing health compelled his retirement in **1949**. He was Vice-Chancellor from **1937** to **1939** and by virtue of this office was a member of the Court of the University, a body to which he was subsequently appointed in

1945 and on which he served until 1948 when he declined re-nomination. He was elected Chairman of Convocation in 1948.

The Principal of the University has kindly supplied the following appreciation. " Throughout the last 23 years of his life he was a well-known figure in University affairs and rendered valued services to the University as an ' elder statesman ' during the last five years of his life. He took a leading part in the discussions of the post-war plans of the University and was Chairman of two important Councils, the Finance and General Purposes Committee and the External Council. In his capacity as Chairman of the External Council he had much to do with the development of more intimate relations between the University and the four university colleges which still take the External degree of the University of London."

Other Services to Education.—He became a member of the Surrey Education Committee, as a representative of London University, when it was reconstituted after the Education Act of 1944, and he served on the Secondary Education and the Further Education Committee and became especially interested in the work of the latter where his advice and knowledge were highly esteemed.

He gave the Committee great help in drawing up and administering their scheme for Award of Major Scholarships and Exhibitions to students taking university courses, and also in planning the expansion of higher technological education in the County.

A development which took place during his period of service was the decision of the County Council to make an annual grant of nearly £30,000 to the University of London.

The Chief Education Officer writes : " It is very unusual for a member who is not a member of the County Council to be selected to Office on the Surrey Education Committee but Sir Robert Pickard was so highly esteemed by his colleagues that they selected him Vice-Chairman of the Further Education Committee."

He served as Honorary Secretary of the teachers' panel of the " Burnham Committee " dealing with salaries for teachers in technical colleges and art schools, 1922—1925, and from 1920 to 1923 was a member of the Consultative Committee of the Board of Education. From 1930 to 1940 he was a Member of Council of Manchester High School for Girls and from 1940 to 1948 Chairman of the Governing Body of Roedean School.

He served as a Member of Council of the Leatherseller's Technical College from 1924 to 1948.

He was also at different times a member of the Courts of the Universities of Birmingham and Manchester.

Royal Institute of Chemistry.—Pickard became a Fellow of the Institute of Chemistry in 1902 and in later years developed a keen interest in its affairs, particularly those concerned with the education and training of chemists. He was a member of its Council during the periods 1923—1926, 1944—1946; Vice-President 1927—1930, 1939—1943; President 1936—1939 and Censor 1936—1944.

During his Presidency he delivered the eighth Gluckstein Memorial Lecture (in 1936) with the title " An Experiment in Co-operative Research in the Cotton and Other Textile Industries " in which he summarised his views and experience as the Director of a large Research Association.

Chemical Society and Chemical Council.—Pickard joined the Chemical Society in 1897 and served on the Council, 1916—1920, 1926—1928, and as Vice-President, 1931—1934, 1937—1940 : he was for many years a very regular attendant at the Society's meetings. The Historical Review of the Chemical Society 1841—1941 states (p. 154) : " In the Society he has for years been a watchful and outspoken critic of its methods and organisation and his criticism has been constructive. He was one of those who proposed the formation of a Reconstruction Committee in 1932 and was its most active member. The various recommendations of this important committee were put into effect and resulted in an extension and an invigoration of the Society's activities. His foresight and experience have been of great value to the Finance and General Purposes Committee, on which he served for several years, and to Council. Directly, in such activities as these, and indirectly as Chairman of the Chemical Council (1931—1938), he had a great influence on the development of the Society in the last decade."

Industrial Research.—Pickard's experience in Lancashire had led him to a deep-rooted belief, to which he frequently gave expression, that the application of the results of fundamental research to industrial processes would result in valuable technological developments, and he told the writer of this Notice that pressure was exerted on him about 1920 to take an active interest in the new Research Association movement. It is certain that the pressure only needed to be gentle to start him off on this course, since his inclinations had been tending in this direction for some time, and his desire for an administrative post of the type afforded by the supervision of a research association had been steadily growing. His recognition that the

undertaking of long-range investigations would constitute an essential part of the work of research associations led to his becoming a champion of co-operative research associations in general.

The growth of the Research Association movement is the most marked development in the organisation of industrial research in this country since the first world war, and there can be no doubt that the movement's present vitality and vigour owe much to Pickard's long participation.

British Leather Manufacturers' Research Association.—In 1920 Pickard, on the strong recommendation of a representative committee, became the first Director of the newly-formed British Leather Manufacturers' Research Association and was quick to seize the opportunities afforded by such an appointment. These activities he combined with his duties as Principal of Battersea Polytechnic which he had assumed earlier in the same year, and his resolution and capacity for work enabled him to do justice to these combined responsibilities.

He now proceeded to transform his beliefs into practice and show how science should be applied to industry. He soon recognised that the histology of hides and skins and the physico-chemical examination of tanning solutions and of proteins were of fundamental significance in attempting to deal with the difficulties which, despite centuries of empiricism, still confront the leather manufacturer, and accordingly he gathered together a highly competent staff of research workers which included the late Dr. D. Jordan-Lloyd amongst its first members.

He soon became convinced that if an industry was to receive substantial benefit from its research association the work of the staff must be made known to and applied by members of the industry, and so visits to works and surveys of processes were arranged and organised. Although he was Director for only 7 years he maintained his connexion with the British Leather Manufacturers' Research Association, in the first place as consultant and later as honorary consultant, until the time of his death.

He was a loyal and devoted servant of the leather industry, pre-eminently as a planner and an organiser, and in these capacities he rendered notable service which has been freely recognised by the industry as a whole: he did not attempt to make any profound contribution to the scientific studies of the research association.

In recognition of his services to education and to the application of scientific research to industrial processes he was elected an Honorary Liveryman of the Leathersellers' Company in 1938.

British Cotton Industry Research Association.—Of Pickard's numerous activities the one with which his name is most closely associated is that of his Directorship of the British Cotton Industry Research Association—a post to which he was appointed at the age of 53 whilst still alert and vigorous, with a varied experience behind him which included an "apprenticeship" of 7 years as Director of the British Leather Manufacturers' Research Association.

When the Directorship of the Cotton Research Association fell vacant in 1927 through the death of Dr. A. W. Crossley the post was advertised but Pickard would not apply. It is no secret that he had felt some disappointment at not being called to fill the position when the Research Association was formed in 1919. Fortunately there were those in Lancashire who realised that Pickard was the man for the post and a deputation came to London and induced him to return to Lancashire. Thus he entered on what proved to be the most fruitful period of his career.

He found that a vast amount of first-class scientific knowledge had been accumulated, but that after six years the industry was getting impatient and looking for more practical results. He saw that the time was opportune for an intensive application of the knowledge already gained and for the introduction of special means to link the scientists more closely and effectively with the practical men from the mills, and in 1928 a liaison officer was appointed and a liaison department formed. At the same time investigations of both a fundamental and a technological character were actively pursued and on a steadily increasing scale, so much so that several extensions of accommodation had to be provided during the ensuing 15 years—including a three-story block of laboratories and a large work room to house weaving machinery, which were formally opened in 1936 by the late Lord Derby.

Pickard tackled with understanding the special difficulties facing the Director of a large research association in an industry divided into several distinct sections, *e.g.*, spinning, weaving, bleaching, and finishing. He came to realise that one important function of such a research association is to envisage the industry as a whole rather than as a collection of component groups of firms with sectional interests and requirements.

The success of his policy taken in combination with the life and vigour he infused into the

Shirley Institute community may be gauged from the fact that when he retired after 17 strenuous years the Research Association was recognised on all sides as an essential part of the textile industry and its name was known throughout the world.

By the time he had retired in 1943 the Shirley Institute with a staff of more than 350, including 80 graduates, had become a splendid organisation in the building up of which he had exerted all his powers of initiative, drive, and administrative ability, and in which he took great pride.

Pickard regarded his stay at the Shirley Institute as the most congenial and productive period of his career—it certainly provided an opportunity where his unusual combination of qualities could be exercised to the full.

In all councils and committees of which he was a member, Pickard expressed his views and opinions with clarity and force—on occasions not unmixed with a modicum of truculence—and was always listened to with attention even by those who disagreed with him. His information on matters of fact was always valuable and there were many occasions on which he was able to draw attention to the terms of Government orders or other official decisions which had escaped the notice of his colleagues but which were highly relevant to the subject under discussion.

He was fond of attending committee meetings and, apart from very occasional lapses into impatience, he was an admirable committee man: the agenda had been carefully studied and pondered on and it was seldom that he failed to contribute at least one useful or constructive suggestion.

During this period of office as Vice-Chancellor of the University of London the Board of Studies in Chemistry gave a dinner in Pickard's honour, at which the late Professor J. C. Philip made the well-received jest "What we all admire about Pickard is his downrightness—not that that excludes uprightness!" Both downrightness and uprightness were indeed the salient qualities of the man.

To the end he was a personality and a man of affairs, frank and fearless in manner. His highly developed critical faculty was in frequent evidence, but in turn he accepted criticism without resentment and usually respected the more highly those who could return some of his critical sallies.

To some his outward bearing was rather aloof or even harsh, but to know him intimately was to recognise a very human man with a high sense of moral values, whose word was his bond.

In 1901 he married Ethel Marian, daughter of Henry Wood of Edgbaston and Dudley and had one son and one daughter. He was created Knight Bachelor in the Coronation Honours of 1937. His family life was a happy one until a few years ago when he suffered two severe blows in the death of his wife and shortly afterwards of his only daughter. He leaves an only son, at whose home in Surrey he died in his sleep.

I am indebted to the Registrar of the Royal Institute of Chemistry, to Dr. F. C. Toy, C.B.E., of the Shirley Institute, and to Dr. H. Phillips, Director of The British Leather Manufacturers' Research Association, for help in the compilation of this notice.

J. KENYON.

JOURNAL OF THE CHEMICAL SOCIETY—1950

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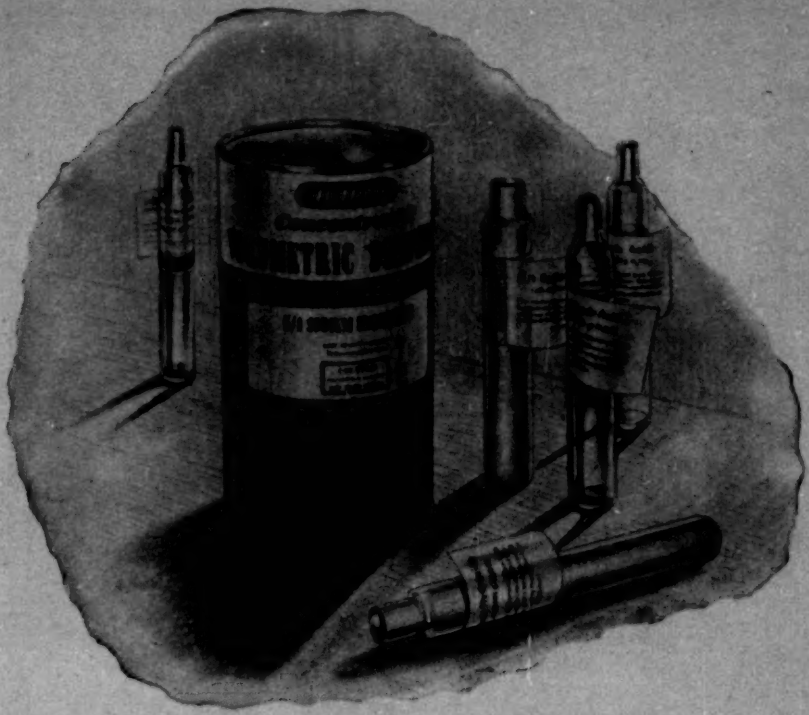

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